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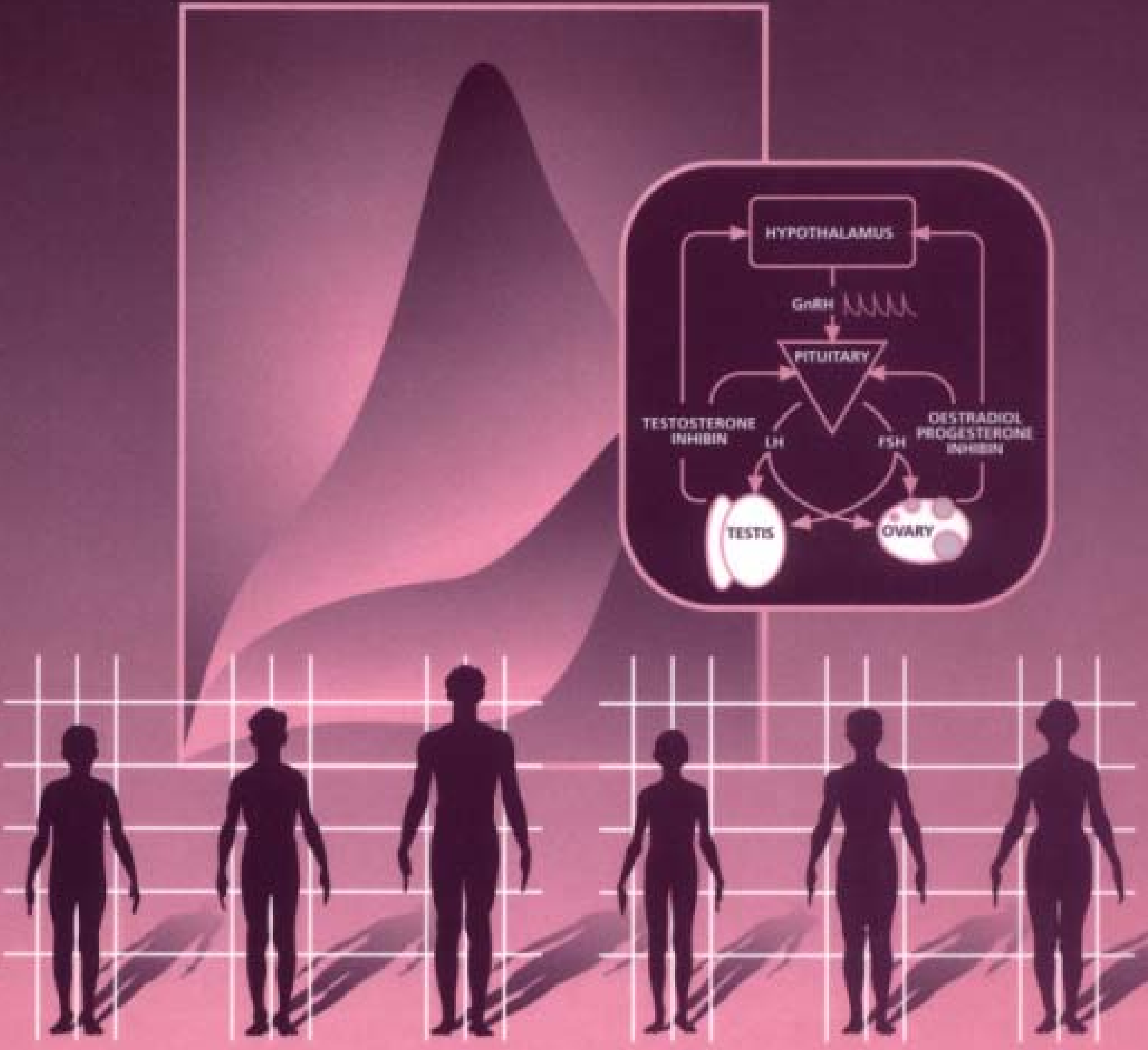
HUMAN GROWTH AND DEVELOPMENT

NOËL CAMERON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HUMAN GROWTH AND DEVELOPMENT

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INTRODUCTION

Noël Cameron

This book has its origins in my own lectures on human growth and development given to undergraduates attending British and South African universities over the last 25 years. In 1976, while studying for my doctoral degree under the supervision of James Tanner at London University's Institute of Child Health, I was asked to give an annual series of lectures to Biological Anthropology students at Cambridge University. The late William Marshall, who had been the "reader" in Tanner's department before taking the professorship and chair in Human Biology at Loughborough University, had previously given these lectures. At about the same time, the geneticist Alan Bittles, then a senior lecturer in Human Biology at Chelsea College, London University, asked me to provide a similar series of lectures to his students.

Faced with the prospect of two series of lectures, I searched the available literature to determine what I could use as sources to write the lectures and what I could recommend to students.

In the 1970s, there were a number of texts, almost exclusively from America, describing the growth and development of children. Ernest Watson and George Lowrey, pediatricians at the University of Michigan Medical School, had first written the *Growth and Development of Children* in 1951.[1] Physical anthropologist and human biologist Stanley Garn, then chairman of the "Physical Growth Department" at the Fels Research Institute in Ohio, collaborated with Israeli pediatrician Zvi Shamir, from Jerusalem, to write *Methods for Research in Human Growth* in 1958.[2] Donald Cheek of Johns Hopkins University wrote *Human Growth: Body Composition, Cell Growth, Energy, and Intelligence*, published in 1968[3]; and the very useful *Child Growth*, by Wilton Krogman, recently retired from the University of Pennsylvania, was published in 1972.[4] In 1966, a landmark work edited by Frank Falkner was destined to be the forerunner to a number of more recent texts in similar style. Called simply *Human Development*, it was, I think, the first volume to use different "authorities" (29 in this case) to provide the breadth and depth required to understand this most diverse of subjects.[5] However, with some notable exceptions, almost all of these volumes had been written by pediatricians interested in the clinical aspects of the subject rather than the biology of growth. In addition to the usual descriptions of the pattern of human growth, they were replete with diagnostic criteria and assessment procedures. They had little in the way of discussion of broader topics and the biological and conceptual basis of growth and development.

In the United Kingdom, Tanner's *Growth at Adolescence,* first published in 1959 and in a second edition in 1962,[6] was, as it is now, *the* classic core text to be supplemented by a variety of scholarly scientific reviews and research papers to cover preadolescent growth and some other areas in greater depth. Later, his *Foetus into Man* (1978)[7] partially made up for this deficit, but it was to some extent an introductory text and there was still the need for greater depth to be added through specific references. In the same year (1978), Frank Falkner collaborated with his friend and previous colleague Jim Tanner to edit the three volume series *Human Growth: A Comprehensive Treatise*,[8] which was an excellent library resource but far too expensive for the undergraduate or graduate student. Clearly by the 1970s many of the earlier texts were becoming dated and my solution was to cite a variety of individual chapters from these various authorities and supplement them with more up to date research papers.

During my sojourn in South Africa, between 1984 and 1997, I lectured to large classes of 400 or more students studying medicine and the allied medical disciplines (dentistry, physiotherapy, occupational therapy, and nursing) in addition to smaller classes of medical science students. The large formal lecture classes presented a relatively restricted opportunity for discussion and the need to portray the biology of human growth in an immediate, vivid way in five or six lectures. The smaller medical science classes allowed me the freedom to "discuss" rather than "teach" human growth and development and to do so in an expansive series of 15 lectures covering half the academic year. By this time, I was invariably recommending Tanner's *Growth at Adolescence* and *Foetus into Man* in addition to specific contributions from Falkner and Tanner's "comprehensive treatise." Barry Bogin's *Patterns of Human Growth* became an accepted alternative text for this audience on its publication in 1988.[9] However, like *Foetus into Man*, it suffered from being written from the perspective and knowledge of a single author and so lacked the breadth, and at times the depth, to be universally recommended.

Out of these experiences came the awareness that a course-work reference text was needed for undergraduate and graduate students but that no single scientist could hope to properly cover the different aspects of human growth and development with the breadth and depth required. Rather, what was needed was a team of lecturers and, if it was to be the best possible text, this team would have to be recognized international experts in their fields of interest. They would indeed be a "dream team" that would, in effect, be invited into the lecture theater to provide a one-hour discourse on their subject. The target audience was the senior undergraduate or immediate postgraduate student; that is, the American graduate student. Therefore, a basic understanding of human biology was expected: human evolution, Mendelian genetics, anatomy, physiology, and descriptive statistics. The text would not only cover the important issues in human growth and development but allow the students the freedom to investigate the subject further through a good annotated reference list and a variety of recommended websites.

Thus, this particular volume was conceived. The contributors were requested to design their manuscript as a lecture that could be given in approximately 60 minutes. Each lecture is augmented by a list of appropriate reference material that the lecturer and students can use to extend any particular aspect of the lecture and provide both breadth and depth to the studies. Most, but not all, lecturers provided a summary or conclusion and some have annotated specific references that they feel contain core information. The limited time for each lecture is based on the duration of a normal university lecture of approximately 60 minutes and forces the lecturer to focus on the essential information. Through the reference list, the lecturer may guide the students toward extending their knowledge.

THE LECTURES AND LECTURERS

The first four lectures provide the core of a course on human growth in which the biological process of growth from birth to adulthood is described. My first chapter forms an introduction to the pattern and biology of human growth and development; the major areas that will be covered by the following 17 chapters.

This broad overview reflects my own breadth of experience and research in human growth and development. Doctoral study supervised by James Tanner at the Institute of Child Health at London University initiated my own background in human growth research. Concurrently, I acted as the clinical auxologist for Tanner's growth disorder clinics at the Hospital for Sick Children, Great Ormond Street, in which I assessed the growth and skeletal maturation of each child attending the clinics. With this dual role, I received probably the best available education and experience in the research techniques applied to both normal and abnormal growth. A lectureship in the same department followed the successful completion of my doctorate, and in time, I found myself being drawn toward the idea of working in a developing country. In this way, I felt that I could put my knowledge and experience to work in a demanding environment in which human growth was the clearest measure of the health and well-being of children.

Keen to put my theory into practice, I went to South Africa in 1984, a time when the black population of that country had experienced almost 40 years of active discrimination. The policy of apartheid had resulted in a society divided not only by color but by differential qualities of health care, access to education, living conditions, and economic empowerment. However, it was clear to those living in South Africa that the end of apartheid was drawing close, and with it, the need for knowledge of the health and well-being of children through information on their growth and development was of primary importance. I initiated two longitudinal studies of rural black children in 1985 and 1986. These set the baseline for comparisons to children in the notorious "township" of Soweto (in fact a city of about 1.5 million people called the "SOuth WEst TOwnship"; hence, Soweto). The national census of 1983 had identified the increasing migration of the black population into urban areas; 14 million were predicted to migrate to urban areas by 2000 and those areas were expected to double in size by 2010. With this realization, the need for relevant up-to-date information on the maternal and child health of these new urban dwellers was intensified; and with clinical and epidemiological colleagues, I initiated the Birth to Ten birth cohort study in 1990. Out of all the births in Soweto and Johannesburg over a 6-week period, over 4000 (74%) were voluntarily enrolled into what is now one of the largest and most detailed studies of child health and growth in the world. Thus, I bring to this book my broad and, I hope, profound experience of normal and abnormal growth in both developed and developing societies and my experience of the assessment of maturity.

Professor Horacio Lejarraga, from Buenos Aires, who provides the second lecture on growth in infancy and childhood, is a pediatric endocrinologist with an interest in child growth that extends over the last 40 years. Having qualified in medicine, he earned a Ph.D. under James Tanner's supervision in London before returning to Argentina to develop an awareness of the importance of human growth among the pediatric community. As president of Argentina's 10,000-strong Society of Paediatrics, he is responsible for Argentina's national growth studies and growth reference charts. Thus, while covering the basic pattern of growth in infancy and childhood, he also brings a clinical perspective to the area of preadolescent growth.

Chapter 3 is provided by Professor Roland Hauspie, from the Free University of Brussels. Hauspie is recognized as an international expert on the mathematical modeling of the human growth curve and plays a prominent role in European auxology. Knowledge of the pattern, magnitude, duration, and variability of adolescent growth was considerably enhanced by modeling techniques, and these are expertly described in Hauspie's lecture.

Peter Ellison, a professor at Harvard College and dean of the Graduate School of Arts and Sciences, is an anthropologist with an international reputation for research on reproductive biology. A spate of recent books (e.g., *On Fertile Ground*[10]) established him as the leading reproductive physiologist of his generation. His chapter on puberty reflects this research interest in addition to demonstrating his strong reputation as a communicator and teacher.

Chapters 5 and 6 address the control of the process of growth through the endocrine system and genetics. Peter Hindmarsh, coauthor of the core text on paediatric endocrinology,[11] has for some time been the leading pediatric endocrinologist at London University's Institute of Child Health. He brings both a biological and clinical approach to the endocrinology of growth. Brad Towne, Ellen Demerath, and Stefan Czerwinski work within America's leading center for human growth research at Wright State University and, in many respects, form the "rising stars" of our dream team. Brad Towne is a physical anthropologist by undergraduate training but an epidemiological and statistical geneticist by postgraduate experience and international reputation. Following a postdoctoral position in the early 1990s with Dr. John Blangero's team at the highly respected Southwest Foundation in Texas, he continues to be closely associated with their work. Ellen Demerath and Stefan Czerwinski are thoroughbred anthropologists, coming from excellent stables. The former is from Harvard and the University of Pennsylvania under the influence of Peter Ellison (Chapter 4) and Francis E. Johnston (Chapter 9), respectively; the latter is from the University of New York and the laboratory of Lawrence M. Schell (Chapter 8) in addition to a recent postdoctoral position at the Southwest Foundation. They provide an excellent and detailed chapter that thoroughly introduces the theory and methods of auxological genetics.

Chapters 7 through 9 examine factors that affect human growth through the environment: nutrition, the physical environment, and the socioeconomic environment. Nick Norgan, my colleague at Loughborough University, first taught me almost 30 years ago, as he began his postdoctoral academic career. He is a human biologist specializing in human energetics and body composition. His international reputation has been founded on population studies in the United Kingdom, Europe, India, Australia, and Papua, New Guinea, and surveys and studies of diet, nutritional status, anthropometry, physical activity, energy expenditure, and body composition. Currently he is the reader in Human Biology at Loughborough University, teaching courses on introductory physiology, the ecology of nutrition, and specialized courses in human energetics. Lawrence Schell has had a distinguished academic career in anthropology. His interest in human growth and, particularly, the effects of environmental stressors began almost 30 years ago, during his doctoral studies under the supervision of Francis E. Johnston at the University of Pennsylvania. At that time, the effect of aircraft noise on the growth, health, and well-being of infants living near airports was his primary concern. Now, he is recognized as the leading authority on the effect of environmental pollutants on human growth. Francis E. Johnston is a giant in the research and teaching on human growth. Falling under the academic influence of Wilton Krogman during his graduate studies, he has since had an enormous influence on the current generation of biologists and anthropologists interested in human growth and development. That influence is evidenced by the fact that five of his former doctoral students contributed to this volume (Bogin, Demerath, Lampl, Schell, and Zemel); and he continues to actively nurture and guide the science of auxology.

Chapters 10 and 11 are specifically aimed at preclinical and clinical students. John S. Parks is a professor of Pediatrics at Emory University and America's leading pediatric endocrinologist. He has a major interest in the genetics underlying and controlling the process of human growth and demonstrates his recognized ability as a teacher within his highly readable chapter. Michael A. Preece is a professor of Child Health and Growth at London University's Institute of Child Health, a position he occupied following the retirement of James M. Tanner. Thus, his academic history within human growth is distinguished. His early contributions were in endocrinology and statistics (particularly mathematical modeling), but later he moved toward molecular genetics and teaches within that theme in this volume.

Chapters 12 through 15 provide insight into specific topics within auxology that I believe should not be excluded from a thorough consideration of the science. The achievement of growth through the process of saltation and stasis was first demonstrated by Michelle Lampl in 1992.[12] I think this discovery is one of the most profound contributions to auxology in the latter part of the last century. It gives focus to the way in which we think about the control of human growth and answers many questions about the relationship between growth at the molecular, cellular, tissue, organ, and whole body levels. Babette Zemel, from the University of Pennsylvania, who writes about body composition and human growth, brings the expertise of both the anthropologist and clinical scientist to bear on this important area. Her early training in human growth was under the supervision of Francis Johnston. Following her doctoral studies in Papua, New Guinea, she became increasingly involved in the assessment of the growth and development of children with clinical disorders—much like my own training with Tanner as a clinical auxologist. Her contributions to our knowledge of the changes in the body composition of children compromised by disease and disorders are internationally recognized. Barry Bogin's *Patterns of Human Growth* was first published in 1988.[9] In some respects, that volume was a vehicle for his evolutionary and biocultural approach to human growth and development and has rightly become a recognized inclusion in university reading lists. Here, he expands specifically on the evolution of the pattern of human growth and, in so doing, raises important questions about how this biological process is modified by evolutionary and environmental forces. Robert M. Malina holds two doctoral degrees, in Anthropology and Physical Education. It is not surprising therefore that his contribution to our knowledge of human growth and development has been in the relationship of exercise to the process of growth and maturation. Recognized as the world authority in this area, his contributions have spanned four decades and given rise to a global awareness of the central role played by exercise in maintaining normal growth.

Finally, Chapters 16 through 19 describe the methodological basis of research in human growth and development: how we assess growth and maturation and how we convert these data to usable growth references and standards. Cameron Chumlea was a student of Robert M. Malina before taking up a position as research scientist at the Fels Research Institute, Wright State School of Medicine, in 1978. He was heavily involved in managing the day-to-day running of the Fels Longitudinal Study, involving anthropometry, body composition, and skeletal maturity assessments. As the Fels Professor in the Departments of Community Health and Pediatrics, his experience is broad and his contributions cover not only human growth but also measurement of the elderly. Tim J. Cole is Britain's leading expert in the statistical analysis of growth data. His LMS method for creating the centiles required for growth reference charts has been accepted throughout the world, and he is in charge of producing the World Health Organization's new growth charts for global use.

USING THIS BOOK

The chapters or lectures within this volume have been designed so that a "core" course can be extracted that provides information on the most important issues. For example, assuming that the first introductory chapter is always included, a class of human biologists or anthropologists would also need the lectures on infancy and childhood, adolescence, and puberty to understand the underlying biology. To these could be added the environmental lectures and the methodological lectures to equip them with the skills for fieldwork. Preclinical or clinical students would need to understand the basic biology but also lectures on endocrinology, growth disorders, and assessment procedures. In this way, a series of lectures can be created to cater to the needs of a variety of audiences, such as medical, allied medical disciplines (physiotherapy, occupational therapy, nursing, etc.), dentistry, anthropology, human biology, education, sports science, sociology, psychology, and any other course dealing with children that will necessarily include information on human growth and development. Almost all the lectures carry their own reference list or bibliography but I have also grouped annotated texts into one section to allow the reader to browse, as if in a bookstore, and glean something of the essence of each book that may be useful.

Final-year students, graduates, and those who have wandered in the vale of academe for many years will appreciate the old adage that "organizing academics is like herding cats." Their very independence of thought and action is what makes them the free thinkers they are. Therefore, to get them all to conform to a specific style is not even a remote possibility. This results in a series of lectures that vary in format. Some lecturers have chosen to lecture as they would present a scholarly textbook chapter; others have been more expansive and less formal. In any case, I consider this variability to be a strength. The student will not be faced by a stereotyped series of lectures just as, in the university lecture theater, no two lecturers are the same.

As editor, I have had the mostly pleasurable experience of seeking some degree of rationality, of attempting to create an ordered series of lectures that would be of major benefit to students and lecturers alike. I thank all the contributors for their willingness to cooperate in this venture and appreciate that most have been under considerable pressure but have nevertheless been timely and gracious in their dealings with me. I thank my friends and colleagues within the science of auxology who have encouraged me to complete this task and hope that their confidence in my ability to produce a worthwhile volume has not been misplaced. Finally, I thank my partner, Anette, and my children Jamie and Beth for their forbearance of my ready willingness to leave them in search of new audiences for my research. This book is dedicated to them, for it would not have been possible without them.

I hope that students find within these pages a biological story that excites and fascinates them as it has me for the last three decades. The process of growth and maturation is one that every living thing in the history of our planet has experienced.

I do not think that the complexity of that process has reached or will reach an end point with *Homo sapiens*, because the process of human growth is constantly dynamic and constantly changing in response to the changes in the environment, both global and local, in which we live. For me, this plasticity, resulting in the wonderfully varied species we see around us, makes the process of human growth so fascinating.

REFERENCES

1. Watson EH, Lowrey GH. Growth and Development of Children. Chicago: Year Book Publishers, 1951.
2. Garn SM, Shamir Z. Methods for Research in Human Growth. Springfield, IL: Charles C Thomas, 1958.
3. Cheek DB. Human Growth: Body Composition, Cell Growth, Energy, and Intelligence. Philadelphia: Lea & Febiger, 1968.
4. Krogman WM. Child Growth. Ann Arbor: University of Michigan Press, 1972.
5. Falkner F (ed). Human Development. Philadelphia: W. B. Saunders Co., 1966.
6. Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.
7. Tanner JM. Foetus into Man. London: Open Books, 1978.
8. Falkner F, Tanner JM. Human Growth: A Comprehensive Treatise. New York: Plenum, 1978.
9. Bogin B. Patterns of Human Growth. Cambridge: Cambridge University Press, 1988.
10. Ellison PT. On Fertile Ground. Cambridge, MA: Harvard University Press, 2001.
11. Brook CGD, Hindmarsh P. Clinical Paediatric Endocrinology, 4th ed. Oxford: Blackwell Scientific Publications, 2001.
12. Lampl M, Veldhuis JD, Johnson ML. Saltation and stasis: A model of human growth. Science. 1992;158:801–803.

1

HUMAN GROWTH CURVE, CANALIZATION, AND CATCH-UP GROWTH

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HISTORICAL BACKGROUND

This introduction to the curve of human growth and development begins in the Age of Enlightenment in eighteenth century France. Between the death of Louis XIV in 1715, and the coup d'état of November 9, 1799, which brought Napoleon Bonaparte to power, philosophy, science, and art were dominated by a movement away from monarchial authority and dogma and toward a more liberal and empirical attitude.[1] Its philosophers and scientists believed that people's habits of thinking were based on irrationality, polluted by religious dogma, superstition, and overadherence to historical precedent and irrelevant tradition. The way to escape from this, to move forward, was to seek for true knowledge in every sphere of life, to establish the truth and build on it. People's minds were, literally, to be "enlightened."[2] Its prime impulse was in pre–Revolutionary France within a group of mostly aristocratic and bourgeois natural scientists and philosophers, who included Rousseau, Voltaire, Diderot (whose *Encyclopedia* was the first literary monument to the Enlightenment), and the Compte de Buffon. Georges Louis LeClerc (Figure 1-1), the Compte de Buffon, was a core member of this group, often known collectively as the *Encyclopedists,* because of their contributions to Diderot's work.

Buffon was born on September 7, 1707, at Montbard in Bourgogne, the provincial capital of Dijon in southwest France. His father, described by the biographer

FIGURE 1-1 Georges Louis LeClerc, Compte de Buffon (1707–1788).

Franck Bourdier as “un homme sans grand charactère,” was a minor parliamentary official married to an older woman, Anne-Christian Martin.[3] She died of tuberculosis when Buffon was only 7 years old. However, an extremely wealthy uncle, Georges Blaisot, had financially favored his niece Anne-Christian, and on her death she left her husband and son with a considerable fortune. Monsieur Leclerc used these funds in 1717 to buy the land of Buffon and the “châtellenie” of Montbard at Dijon. Georges Louis was educated by the Jesuits at the Colleges de Godran, where he demonstrated an aptitude for mathematics. In 1728, he moved to the University of Angers and thence suddenly to England following a duel with an officer of the Royal-Croates over “une intrigue d’amour.” He traveled in Switzerland, France, and Italy during the next 4 years, returning to Dijon in 1732 to reach a financial settlement with his father, with whom he had long argued following the latter’s remarriage. He inherited his maternal ancestral estate at Montbard and divided his time between Paris and the country, pursuing his interests in mathematics, natural science, and sylviculture. By the age of 32, he was recognized as the premier horticulturist and arborealist in France and was appointed by King Louise XV as the director of the Jardin du Roi in 1739. This position was the equivalent of being the chief curator of the Smithsonian Institution or the British Museum of Natural History—it was the most prestigious governmental scientific position in the “natural sciences” that Buffon could have obtained. During the next few years, Buffon started to work on an immense project that was to include all that was known of natural history. *Histoire Naturelle, Générale et Particulière* would be a vast undertaking, but one that Buffon, who from all accounts was a man of no small ego, appears to relish and that, by his death, was composed of 36 volumes. There were 15 volumes on quadrupeds (1749–1767), 9 on birds (1770–1783), 5 on minerals (1783–1788), and 7 “supplementary volumes.” Eight further volumes prepared by E. de Lacepede were added posthumously between 1788 and 1804 and included two volumes on reptiles (1788–1789), five on fish (1798–1803), and one on *Cetacea* (1804). However, the supplement to volume 14, published in 1778, is particularly interesting to us.

On page 77 of this supplement is the record of the growth of a boy known simply as De Montbeillard’s son. The friendship between Philibert Geuneau De Montbeillard and Buffon had been secured by a common interest in the natural sciences. Between 1770 and 1783, De Montbeillard coauthored the nine volumes of *Histoire Naturelle* devoted to birds. He was also a correspondent of Diderot and clearly recognized as one of the Encyclopedists. Given the desire of these central scientific figures of the Enlightenment to measure and describe the natural world as it is and to find the truth, it is not too surprising that De Montbeillard would take an empirical interest in the growth of his own son. Nor is it inconceivable that his friend and colleague Buffon would wish to include this primary evidence of the course of human growth within his opus magnum.

De Montbeillard had been measuring the height of his son about every 6 months from his birth in 1759 until he was 18 years of age in 1777. The boy’s measurements of height were reported in the French units of the time: pieds, pouces, and lignes, which correspond roughly to present day units as a foot, inch, and 12th part of an inch. (Tanner,[4] p. 470, notes that, "The Parisian *pied*, or foot, divided into 12 pouces, or inches, each divided into 12 lignes, was longer than the English foot. Isaac Newton . . . found 1 *pied* equal to 12.785 inches, but the later official conversion, on the introduction of the metre, gave it as 12.7789 inches. The *pouce*, then, equals 2.71 cm whereas the English inch equals 2.54 cm.")

Not until an American anatomist, R. E. Scammon, at the University of Minnesota, translated these measurements into centimeters and his results were published in the *American Journal of Physical Anthropology* under the title "The First Seriatim Study of Human Growth," could we look on the growth of De Montbeillard's son in the form of a chart.[5]

THE DISTANCE CURVE OF GROWTH

By joining together the data points at each age, Scammon produced a curve that described the height achieved at any age, which became known as a *height distance* or *height-for-age curve* (Figure 1-2). We use the term *distance* to describe height achieved, because it is easy to visualize and understand that a child's height at any particular age is a reflection of how far that child has progressed toward adulthood. It embodies the sense of an ongoing journey that we are, as it were, interrupting to take a "snapshot." The resulting curve is interesting for a number of reasons. First, when growth is measured at intervals of 6 months or a year, the resultant curve is a relatively smooth and continuous process. It is not characterized by periods of no growth and then by dramatic increases in stature. Second, growth is not a *linear* process. We do not gain the same amount of height during each calendar year. Third, the curve of growth has four distinct phases (or five if we include the mid-growth spurt, see later), corresponding to relatively rapid growth in infancy, steady growth in childhood, rapid growth during adolescence, and very slow growth as the individual approaches adulthood. Fourth, growth represents a most dramatic increase in size. De Montbeillard's son, for instance, grew from about 60 cm at birth to over 180 cm at adulthood. The majority of that growth occurs during infancy and childhood, but perhaps the most important physical changes occur during adolescence. Fifth, we cease growing, or reach adult height, during our late teenage years, at 18 or 19 years of age.

The pattern of growth that we see from this curve is a function of the frequency of data acquisition. For instance, if we were to measure a child only at birth and at 18 years, we might believe, by joining up these two data points, that growth was a linear process. Clearly, the more frequently we collect data, the more we can understand about the actual pattern of growth on a yearly, monthly, weekly, or even daily basis. Naturally, such high-frequency studies are logistically very difficult, and therefore only a very few are in existence. The most important is probably that of Lampl, Veldhuis, and Johnson, who were able to assess growth in length,

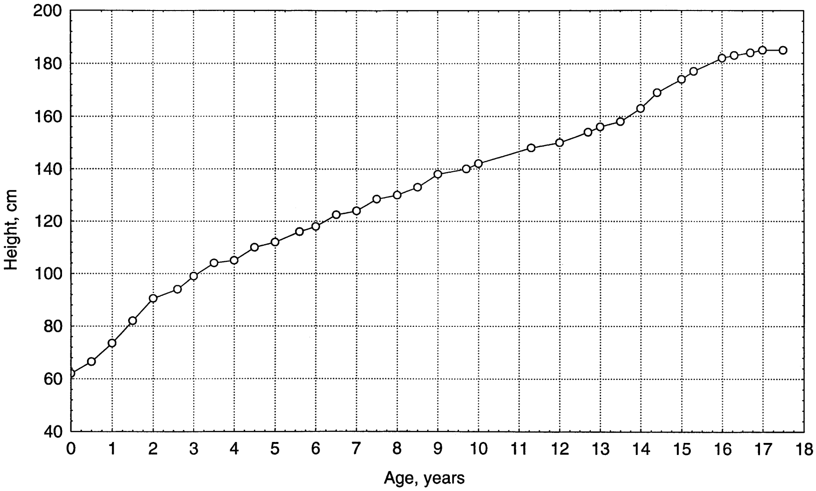

FIGURE 1-2 The growth of De Montbeillard's son 1759–1777: Distance. (Redrawn from Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

weight, and head circumference on a sample of 31 children on daily, biweekly, and weekly measurements.[6] The resulting data demonstrated that growth, in height at least, may not be a continuous phenomenon but actually occur in short bursts of activity (saltation) that punctuate periods of no growth (stasis) (see Chapter 12). However, the data we have for De Montbeillard's son was collected approximately every 6 months and thus, at best, can tell us only about half-yearly or yearly patterns of growth.

It is clear that the pattern of growth that results from these 6-monthly measurements is composed of several different curves. During "infancy," between birth and about 5 years old, there is a smooth curve that we can describe as a "decaying polynomial," because it gradually departs negatively from a straight line as time increases. During childhood, between 5 and about 10 years old, the pattern does not depart dramatically from a straight line. This pattern changes during adolescence, between about 10 and 18 years old, into an S-shaped, or sigmoid, curve, reaching an asymptote at about 19 years old.

The fact that the total distance curve may be represented by several mathematical functions allows us to apply mathematical "models" to the pattern of growth. These models are parametric functions that contain constants, "parameters." Once we have found an appropriate function that fits the raw data, we can analyze the parameters and, by so doing, learn a good deal about the process of human growth (see Chapter 3). For instance, in the simplest case of two variables, such as age (X) and height (Y), being linearly related between, say, 5 and 10 years of age (i.e., a constant unit increase in age is related to a constant unit increase in height), the mathematical function $Y = a + bX$ describes their relationship. The parameter a represents the point at which the straight line passes through the Y-axis and is called the *intercept*; b represents the amount that X increases for each unit increase in Y and is called the *regression coefficient*. Fitting this function to data from different children and subsequent analysis of the parameters can tell us about the magnitude of the differences among the children and lead to further investigations of the causes of the differences. Such time series analysis is extremely useful within research on human growth because it allows us to reduce large amounts of data to only a few parameters. In the case of De Montbeillard's son, 37 height measurements were made at 37 different ages, yielding 74 data items for analysis. The fitting of an appropriate parametric function, such as the Preece-Baines function,[7] which we discuss later (see Chapter 3), reduces these 74 items to just 5. Because of their ability to reduce data from many to only a few items, such parametric solutions are said to be parsimonious and are widely used in research into human growth.

THE VELOCITY GROWTH CURVE AND GROWTH SPURTS

The pattern created by changing rates of growth is more clearly seen by actually visualizing the rate of change of size with time; that is, "growth velocity," or in this particular case, "height velocity." The term *height velocity*, coined by Tanner,[8] was based on the writings of D'Arcy Wentworth Thompson (1860–1948). D'Arcy Thompson was a famous British natural scientist, who published a landmark biology text, *Growth and Form*, in 1917 with a second edition in 1942.[9,10] In the later edition (p. 95), Thompson wrote that, while the distance curve "showed a continuous succession of varying *magnitudes,*" the curve of the rate of change of height with time "shows a succession of varying *velocities*. The mathematicians call it a *curve of first differences*; we may call it a curve of the rate (or rates) of growth, or more simply a *velocity curve*." The velocity of growth experienced by De Montbeillard's son is displayed in Figure 1-3. The Y-axis records height gain in cm/yr^{-1}; and the X-axis is the chronological age in years. We see that, following birth, two relatively distinct increases in growth rate occur at 6–8 years and again at 11–18 years. The first of these "growth spurts" is called the *juvenile* or *mid-growth spurt* (see Chapter 2) and the second is called the *adolescent growth spurt* (see Chapter 3).

There is, in fact, another growth spurt that we cannot see because it occurs prior to birth. Between 20 and 30 weeks of gestation, the rate at which the length of the fetus increases reaches a peak at approximately 120 cm/yr^{-1}, but all we can observe postnatally is the slope of decreasing velocity lasting until about 4 years of age. Similarly, increase in weight also experiences a prenatal spurt but a little later, at 30–40 weeks of gestation. Of course, information on the growth of the fetus is difficult to obtain and relies largely on two sources of information: extrauterine anthropometric measurements of preterm infants and intrauterine ultrasound measurements of fetuses. Ultrasound assessments of crown-rump length indicate that

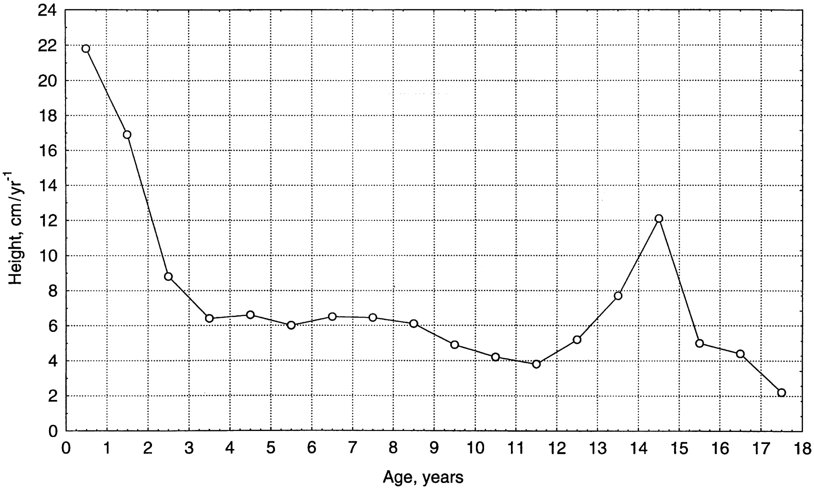

FIGURE 1-3 The growth of De Montbeillard's son 1759–1777: Velocity. (Redrawn from Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

growth is smooth and rapid during the first half of pregnancy. Indeed, it is so smooth between 11 and 14 postmenstrual weeks, when the growth velocity is 10–12 mm/week^{-1}, gestational age can be calculated from a single measurement to within ±4.7 days. The 95% error band when three consecutive measurements are taken is ±2.7 days. Intrauterine growth charts for weight demonstrate that growth over the last trimester of pregnancy follows a sigmoid pattern and, like the sigmoid pattern reflected in height distance at adolescence, demonstrates a growth spurt when velocity is derived. The spurt should reach a peak at about 34–36 weeks. Why should the fetus be growing so quickly in terms of weight at this time? Results from an analysis of 36 fetuses in the mid-1970s demonstrated that, between 30 and 40 postmenstrual weeks, fat increases from an average of 30 g to 430 g. This dramatic accumulation of fat is directly related to the fact that fat is a better source of energy per unit volume than either protein or carbohydrate. Therefore, a significant store of energy is available to the fetus for the immediate postnatal period.

While the prenatal spurt and juvenile growth spurt may vary in magnitude, they seem to occur at roughly the same age, both within and between the sexes. The adolescent growth spurt, however, varies in both magnitude and timing within and between the sexes: Males enter their adolescent growth spurt almost 2 years later than females and have a slightly greater magnitude of height gain. The result is increased adult height for males, mainly resulting from their 2 years of extra growth prior to adolescence. At the same time, other skeletal changes are occurring that result in wider shoulders in males and, in relative terms, wider hips in females. Males demonstrate rapid increases in muscle mass and females accumulate greater amounts of fat. Their fat is distributed in a "gynoid" pattern, mainly in the gluteofemoral region, rather than in the "android" pattern, with more centralized distribution characteristics of males (see Chapter 13). Physiologically, males develop greater strength and lung capacity. Thus, by the end of adolescence, a degree of morphological difference exists between the sexes: Men are larger and stronger and more capable of hard physical work. Such sexual dimorphism is found to a greater or lesser extent in all primates and reminds us that these physical devices had, and perhaps still have, important sexual signaling roles (see Chapter 14).

In addition to dramatic growth during adolescence, increased adult size in men is also achieved because of the extended period of childhood growth. This period of childhood is peculiar to the *human* child, and its existence raises important questions about the evolution of the *pattern* of human growth. Theoretical work on this evolution has been done recently by Barry Bogin at the University of Michigan. He argues (see Chapter 14) that humans have a childhood because it creates a reproductive advantage over other species through the mechanism of reduced birth spacing and greater lifetime fertility. In addition, slow growth during childhood allows for "developmental plasticity" in sympathy with the environment, with the result that a greater percentage of human young survive than the young of any other mammalian species.

OTHER PATTERNS OF GROWTH

The pattern of growth in height, as demonstrated by De Montbeillard's son, is only one of several patterns of growth found within the body. Figure 1-4 illustrates the major differences in pattern as exemplified by neural tissue (brain and head), lymphoid tissue (thymus, lymph nodes, intestinal lymph masses), and reproductive tissue (testes, ovaries, epididymis, prostate, seminal vesicles, Fallopian tubes) in addition to the general growth curve of height or weight and some major organ systems (respiratory, digestive, urinary). The data on which this figure is based are old, having originally been reported by R. E. Scammon in 1930,[11] but they are sufficient to allow us to appreciate that lymphoid, neural, and reproductive tissue have patterns of growth very different from the general growth curve we initially observed. Neural tissue exhibits strong early growth and is almost complete by 8 years of age, while reproductive tissue does not really start to increase in size until 13 or 14 years of age. The lymphatic system, which acts as a circulatory system for tissue fluid and includes the thymus, tonsils, and spleen in addition to the lymph nodes, demonstrates a remarkable increase in size until the early adolescent years, then declines, perhaps as a result of the activities of sex hormones during puberty (see Chapters 4 and 5). The majority of our interest in this and other issues on growth concerns the pattern of growth as exhibited by height and weight; that is, the "general" pattern in Figure 1-4. It is clear, however, that research on the growth of neural tissue must be targeted at fetal and infant ages and research on the growth of reproductive tissue on adolescent or teenage years when growth is at a maximum.

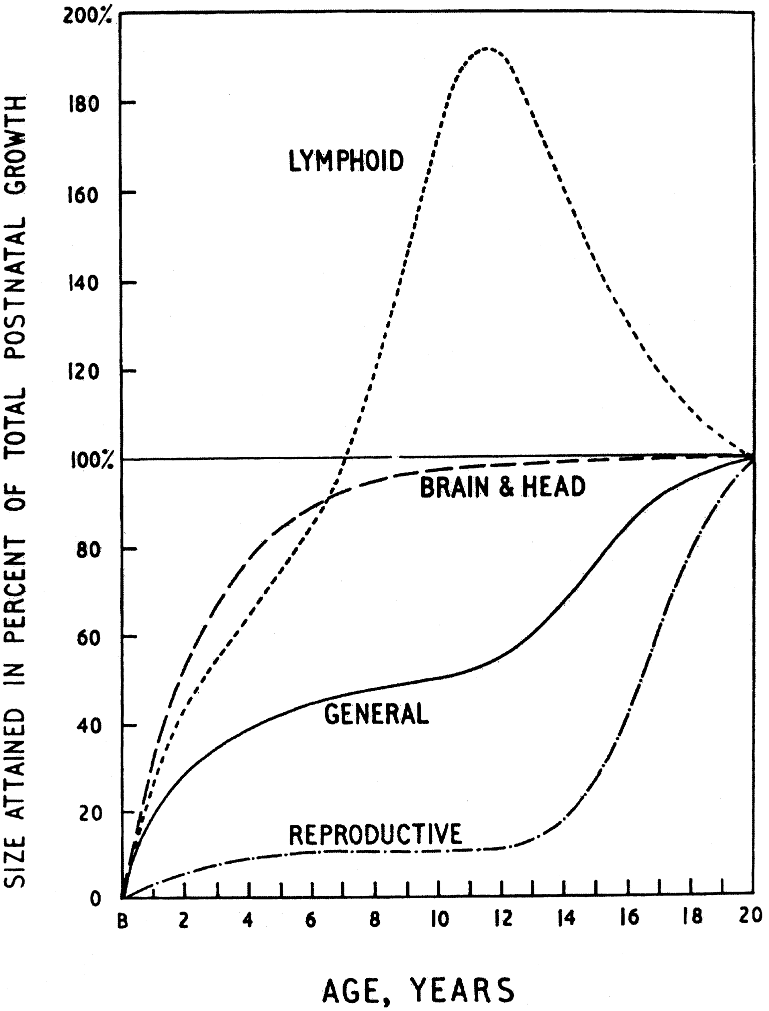

FIGURE 1-4 Growth curves of different parts and tissues of the body, showing the four main types: lymphoid (thymus, lymph nodes, intestinal lymph masses); brain, neural tissue, and head (brain and its parts, dura, spinal cord, optic system, cranial dimensions); general tissue (whole body linear dimensions, respiratory and digestive organs, kidneys, aortic and pulmonary trunks, musculature, blood volume); reproductive tissue (testes, ovary, epididymis, prostate, seminal vesicles, Fallopian tubes). (From Tanner JM. Growth at Adolescence. Oxford: Blackwell Scientific Publications, 1955.)

GROWTH VERSUS MATURITY

Although we have concentrated on the growth of one boy in eighteenth century France, De Montbeillard's son, it is now evident that his curves of growth (i.e., distance and velocity) reflect patterns found in all children who live in normal environmental circumstances. We may differ in the magnitude of growth that occurs as is evident from our varying adult statures, but to reach our final height, we all experience a similar pattern of human growth to a greater or lesser degree. It is evident that growth in height is not the only form of somatic growth that occurs in the human body. We already discussed that, as we experience the process of growth in linear dimensions (i.e., as we get taller), we also experience other forms of growth. We get heavier, fatter, and more muscular; and we experience changes in our body proportions. In addition, we become more "mature" in that we experience an increase in our functional capacity with advancing age, which may be evidenced in our increasing ability to undertake physical exercise in terms of both magnitude and duration (see Chapter 15). Although we tend to think of "growth and development" as a single biological phenomenon, both aspects have distinct and important differences. *Growth* is defined as an increase in size, while *maturity* or *development* is an increase in functional ability. The end point of growth is the size we attain by adulthood, roughly corresponding to growth rates of less than 1 cm/yr^{-1}, and the end point of maturity is when we are functionally able to successfully procreate. This involves not simply to be able to produce viable sperm in the case of men and viable ova in the case of women. Successful procreation in a biological sense requires that the offspring survive so that they may also procreate. Therefore, successful maturation requires not just biological maturity but also behavioral and perhaps social maturity.

The relationship between somatic growth and maturity is perhaps best illustrated by Figure 1-5. The figure shows three boys and three girls who are of the same ages within gender: The boys are exactly 14.75 years old and the girls 12.75 years old. The most striking feature of this illustration is that, even though they are the same age, they demonstrate vastly different degrees of maturity. The boy and girl on the left are relatively immature compared to those on the right. To be able to make these distinctions in levels of maturity, we must use some assessments of maturation, "maturity indicators" (see Chapter 17). These may well include the obvious development of secondary sexual characteristics (breast and pubic hair in girls and genitalia and pubic hair in boys), in addition to dramatic changes in body shape, increases in muscularity in boys and increases in body fat in girls. If we look carefully, we see that distinct changes in the shape of the face also occur, particularly in boys, which result in "stronger" features compared to the rather soft outline of the preadolescent face. However, the maturity indicators we use to assess maturation for clinical and research purposes are constrained by the need to demonstrate "universality"—they must appear in the same sequence within both sexes—and similarity in both beginning and end stages. Because human size is governed by factors other than the process of maturation, we cannot use an absolute size to determine maturation. Even though, in very general terms, someone who is large is likely to be older and more mature than someone who is small, it is apparent from Figure 1-4 that, as the two individuals approach each other in terms of age, this distinction becomes blurred. We therefore use the appearance and *relative* size of structures rather than their *absolute* size to reflect maturity. The most common

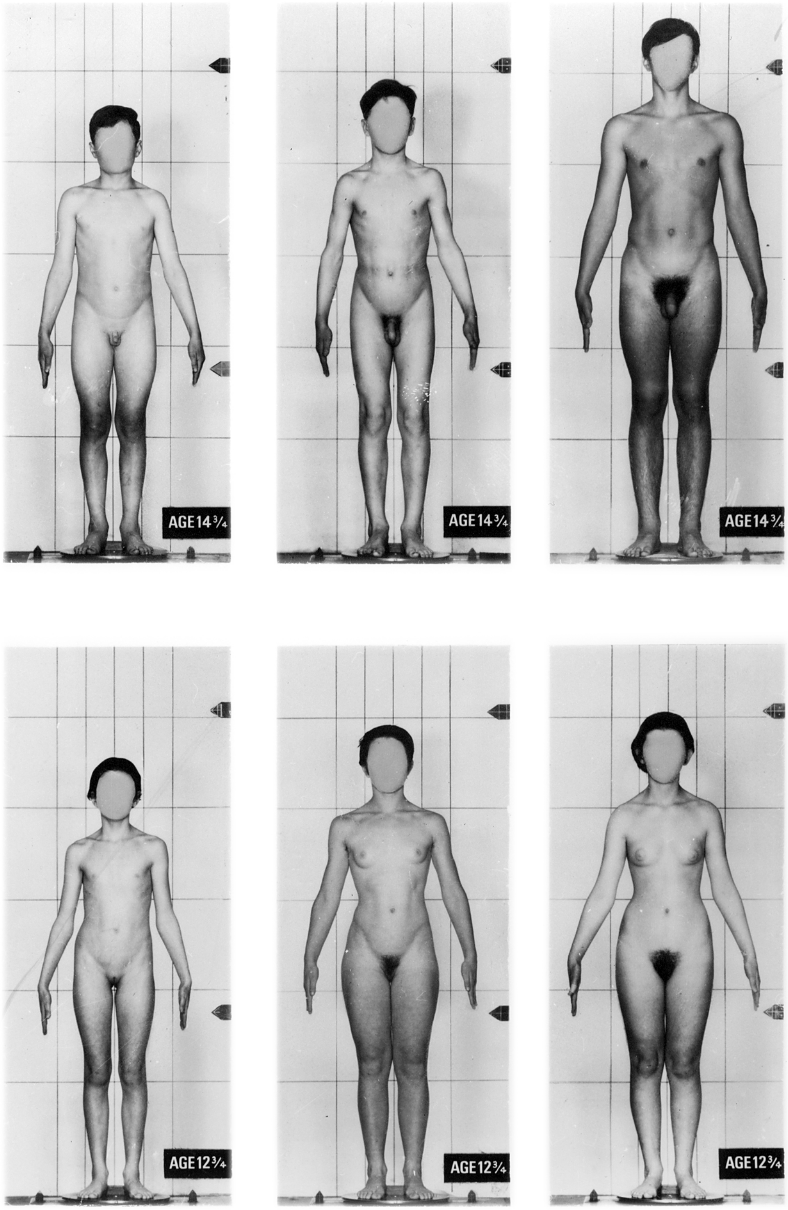
AGE 14¾
AGE 14¾
AGE 14¾
AGE 12¾
AGE 12¾
AGE 12¾

FIGURE 1-5 Three boys and three girls photographed at the same chronological ages within sex: 12.75 years for girls and 14.75 years for boys. (From Tanner JM. Growth and endocrinology of the adolescent. In: Gardner L (ed). Endocrine and Genetic Diseases of Childhood, 2nd ed. Philadelphia: W. B. Saunders, 1975.)

maturity indicators are secondary sexual development, skeletal maturity, and dental maturity (see Chapter 17).

THE CONTROL OF GROWTH

Clearly, the process of human growth and development, which takes almost 20 years to complete, is a complex phenomenon. It is under the control of both genetic and environmental influences, which operate in such a way that, at specific times during the period of growth, one or the other may be the dominant influence. At conception, we obtain a genetic blueprint that includes our potential for achieving a particular adult size and shape. The environment alters this potential. Clearly, when the environment is neutral, when it is not exerting a negative influence on the process of growth, the genetic potential can be fully realized. However, the ability of environmental influences to alter genetic potential depends on a number of factors, including the time at which they occur; the strength, duration, and frequency of their occurrence; and the age and gender of the child (see Chapter 9).

The control mechanism that environmental insult affects is the endocrine system. The hypothalamus or "floor" of the diencephalon, situated at the superior end of the brain stem, coordinates the activities of the neural and endocrine systems. In terms of human growth and development, its most important association is with the pituitary gland, which is situated beneath and slightly anterior to the hypothalamus. The rich blood supply in the infundibulum, which connects the two glands, carries regulatory hormones from the hypothalamus to the pituitary gland. The pituitary gland has both anterior and posterior lobes. The anterior lobe, or adenohypophysis, releases the major hormones controlling human growth and development: growth hormone, thyroid-stimulating hormone, prolactin, the gonadotrophins (luteinizing and follicle-stimulating hormones), and adrenocorticotrophic hormone (see Chapters 4 and 5). Normal growth does not depend simply on an adequate supply of growth hormone but is the result of a complex and at times exquisite relationship between the nervous and endocrine systems. Hormones rarely act alone but require the collaboration or intervention of other hormones to achieve their full effect. Therefore, growth hormone causes the release of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 directly affects skeletal muscle fibers and cartilage cells in the long bones to increase the rate of uptake of amino acids and incorporate them into new proteins, thus it contributes to growth in length during infancy and childhood. At adolescence, however, the adolescent growth spurt will not occur without the collaboration of the gonadal hormones: testosterone in boys, estrogen in girls.

There is ample evidence from research on children with abnormally short stature that a variety of environmental insults disturb the endocrine system, causing a reduction in the release of growth hormone. However, other hormones are also affected by such insults, making the diagnosis of growth disorders a complex and engrossing series of investigations that increasingly requires an appreciation of both genetic and endocrine mechanisms (see Chapters 5, 10, and 11).

GROWTH REFERENCE CHARTS

The growth of De Montbeillard's son is interesting, not only because he depicts a normal pattern of growth but also because he achieved an adult height that was over 180 cm, or about 6 feet. He was quite tall for a French man in the eighteenth century. How do we know that someone is "tall" or "short"? What criteria do we use to allow us to make such a judgment? Those not involved in the study of human growth make such a judgment based on their exposure to other people. If, for instance, they have lived only among the pygmies of Zaire, then anyone over 165 cm (5 ft, 5 in.) would be very tall. If, on the other hand, they had lived only among the tall Nilotic tribesmen of North Africa, anyone less than 175 cm (5 ft, 9 in.) would be unusually small. Most of us live in regions of the world in which the majority of people have adult heights that lie between these extremes and view average adult heights at about 178 cm (5 ft, 10 in.) for men and 170 cm (5 ft, 7 in.) for women as "normal." Of course, adult heights range about these average values and that range gives us an estimate of the normal variation in adult stature. Beyond certain points in that range, we begin to think of an individual's height as either "too tall" or "too short." This is also true of the heights of children during the process of growth. Each age from birth to adulthood has a range of heights that reflects the sizes of normal children; that is, children who have no known disease or disorder that adversely affects height (e.g., bone dysplasias, Turner syndrome). To assess the normality or otherwise of the growth of children, we use growth reference charts. These charts depict both the average height to be expected throughout the growing years (typically from birth to 18 years) and the range of normal heights, in the form of percentile (centile) distributions.

Figure 1-6 is such a reference chart. It depicts the normal range of heights for British boys from 4 to 18 years old. The normal range is bound by outer centile limits of the 0.4th and 99.6th centiles. Therefore, "normal" heights are thought of as heights that fall between these limits; although, of course, 0.8% of normal children will have heights below the 0.4th or above the 99.6th centile (see Chapter 18). The illustrated centiles have been chosen because they each equate roughly to 0.67 *Z*-scores or standard deviation (SD) scores from the 50th centile or average values. Hence, the 25th centile is 0.675 *Z*-scores below the mean, the 10th centile is 1.228, and the 2nd centile is 1.97. Their importance is that, not only do they provide a reasonable point at which to investigate possible abnormalities of growth, but they also provide reasonable guidelines for how we expect growth to proceed within the normal range. It has recently been suggested, for instance, that a child whose growth exhibits a movement of 0.67 *Z*-scores is exhibiting a clinically significant response to the alleviation of some constraining factor (see "catch-up"

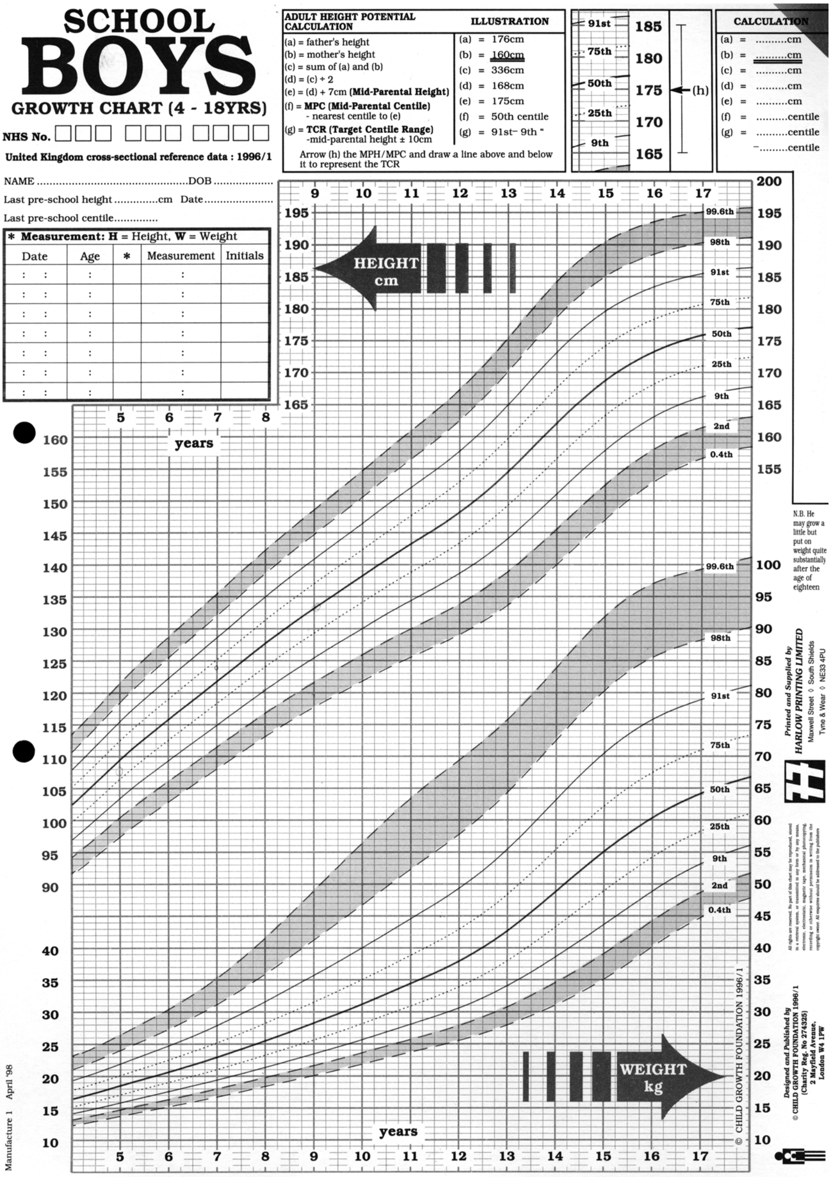

FIGURE 1-6 Growth reference chart for U.K. boys from 4 to 18 years old (© Child Growth Foundation).

growth, later).[12] So, the movement of a child's height or weight upward through the centiles from the 10th to the 25th or downward from the 98th to the 75th can be viewed by clinicians as more than simply a chance occurrence.

Children who have no constraints on their growth exhibit patterns of growth that fall steadily and continuously parallel to the centile lines prior to adolescence. However, as the adolescent growth spurt takes place, they depart from this parallel pattern, and all adolescents demonstrate “centile crossing.” In “early developers,” the height-for-age curve rises through the centiles before their peers and levels off early, as they achieve their adult stature. “Late developers,” on the other hand, initially appear to fall away from their peers as the latter enter their growth spurts, and then accelerate into adolescence rising through the centile lines when their peers have ceased or nearly ceased growing. Even the child who enters their growth spurt at the average age for the population crosses centile lines. This is because the source data for these reference charts were collected in cross-sectional studies: studies in which children of different ages were measured on a single occasion. They thus reflect the average heights, weights, and the like of the population rather than the growth of an individual child. If one were able to undertake a growth study of the same children over many years (a longitudinal study), one could theoretically adjust the data so that it illustrated the adolescent growth spurt of the average child; that is, the child experiencing the adolescent growth spurt at the average age. In such a hypothetical situation, the growth curve of the average child would fall exactly on the 50th centile line. But that is not the case with growth reference charts based on cross-sectional data. The average child initially falls away from the 50th centile line as he or she enters the growth spurt and then crosses it at the time of maximum velocity (peak velocity) before settling back onto the 50th centile as he or she reaches adult height.

Figure 1-7 illustrates the typical growth patterns exhibited by early, average, and late developers. The early developing girl (E) accelerates into adolescence at about 8 years old, some 2 years prior to the average, and rapidly crosses centile lines to move from just above the 50th to the 90th centile. However, her growth slows at about 13 years and her height centile status falls back to the 50th centile. Conversely, the late developer (L) is almost 13 years old before she starts to accelerate, and that delay causes her height centile status to fall from the 50th to below the 10th centile before rising to the 50th centile as she approaches adulthood. Finally, the average girl initially falls away from the 50th centile but then accelerates through it at the average age of peak velocity before following the 50th centile as adulthood is reached.

CANALIZATION

Figure 1-7 demonstrates more than simply the crossing of centiles by early and late developers. It also tells us something about the control of human growth. These are not hypothetical curves. They are the growth curves of real children who were measured on a 6- or 3-month basis throughout childhood and adolescence.[13] Note that, during childhood, they were growing on or near to the 50th centile, and after the deviations brought about by their adolescent growth spurts, they returned to that same centile position in adulthood. Such adherence to particular centile positions

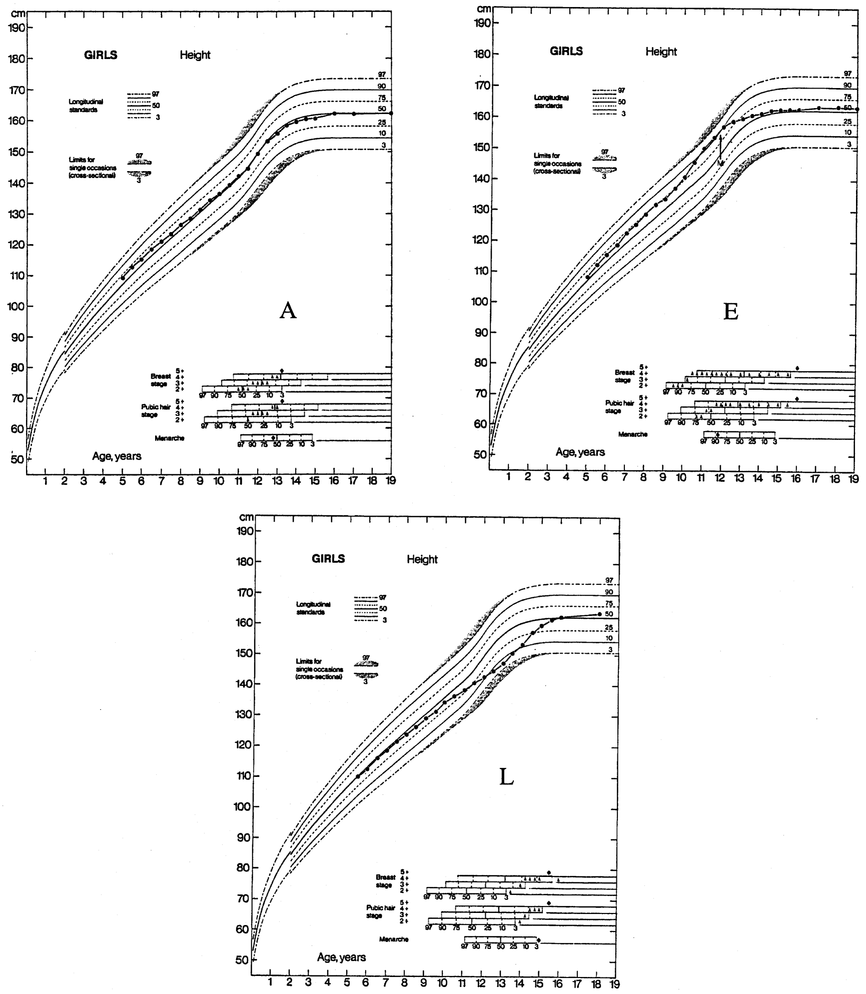

FIGURE 1-7 Growth curves of average (A), early (E), and late (L) developers. (Data from numbers 35, 38, 45 in Tanner JM, Whitehouse RH. Atlas of Human Growth. London: Academic Press, 1980.)

is found time and again when one studies the growth of children. Indeed, it is true to say that all children, when in an environment that does not constrain their growth, exhibit a pattern of growth that is more or less parallel to a particular centile or within some imaginary "canal." This phenomenon was described by a British geneticist, C. H. Waddington, in 1957,[14] and has been termed *canalization* or *homeorrhesis*. It is most likely that this pattern is genetically determined and that growth is target seeking, in that we have a genetic potential for adult stature and the process of growth, in an unconstrained environment, takes us inexorably toward that target.

CATCH-UP GROWTH

However, none of us has lived or been brought up in a completely unconstrained environment. Toward the end of our intrauterine life, our growth was constrained by the size of the uterus. During infancy and childhood, we succumbed to a variety of childhood diseases that caused us to lose our appetite and at those times our growth would have reflected the insult by appearing to slow down or, in a more severe case, to actually cease.

Waddington[14] likens growth to the movement of a ball rolling down a valley floor. The sides of the valley keep the ball rolling steadily down the central course (point A in Figure 1-8). If an insult occurs, it tends to push the ball out of its groove or canal and force it up the side of the valley (point B). The amount of deviation from the predetermined pathway depends on the severity and duration of the insult. However, every insult causes a loss of position and a reduction in growth velocity, as the ball is confronted by the more severe slope of the valley wall. The magnitude of the loss of velocity also depends on the severity and duration of the insult. Thus, a small insult of short duration causes a slight shift onto the valley sides, which entails a minor change in velocity. The alleviation of the insult results in a rapid return to the valley floor at an increased velocity (point C). Having reached the floor normal growth velocity is resumed (point D).

This analogy may be seen to apply appropriately to the process of human growth. Figure 1-9 shows the growth chart of a girl who has suffered from celiac syndrome.[13] In this condition, an abnormality of the lining of the gut impedes absorption of food, resulting in the child being starved. The result in terms of growth is that the height velocity is gradually reduced as the malnutrition becomes more and more severe. The reduction in height velocity means that the height distance curve leaves the normal range of centiles and the child becomes abnormally short for her age. So, at the age of almost 12 years, she is the average height of a 5-year-old. On diagnosis the child is switched to a gluten-free diet, which alleviates the malabsorption. Recovery of height velocity is rapid and jumps from 1 cm/yr^{-1} to 14 cm/yr^{-1}, returning the child to the normal range of centiles within 3 years. Indeed, this girl ends up within the range of heights one would expect given the heights of her parents. So she demonstrates "complete" catch-up growth, in that she returns to the centile position from which she most probably started.

Catch-up growth is not always complete, however, and appears to depend on the timing, severity, and duration of the insult. This appears to be particularly true in the treatment of hormone deficiencies. Initial diagnosis is often delayed until the child is seen in relation to other children and the deficiency in stature becomes obvious. Usually a hormone deficiency, such as growth hormone deficiency, is accompanied by a delay in maturation. Response to treatment appears to depend

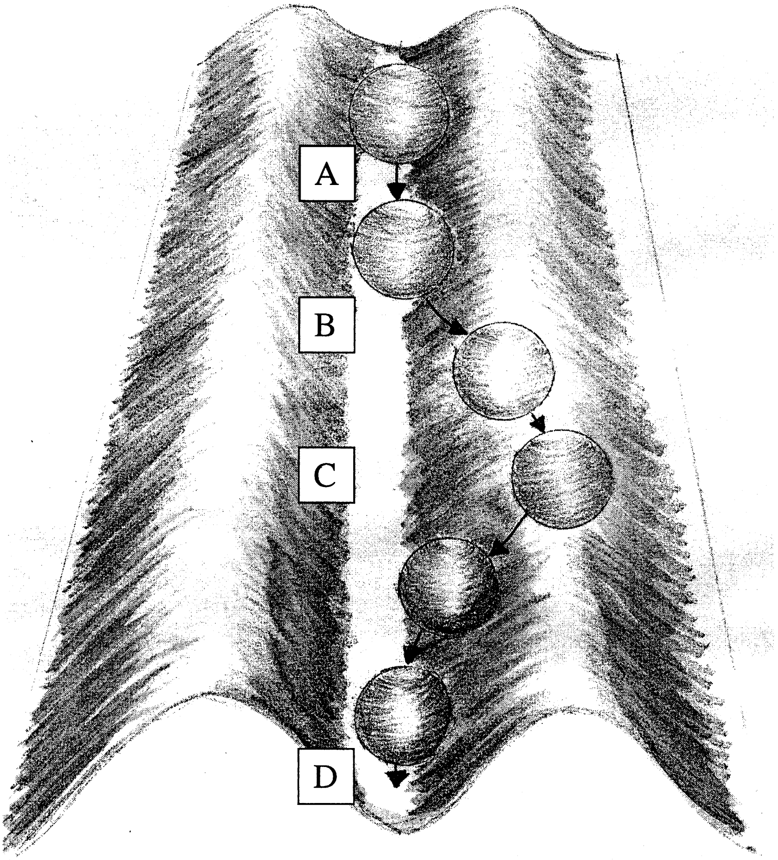

FIGURE 1-8 A pictorial illustration of the phenomenon of canalization. A = normal canalized growth; B = the point at which an impact causes the ball to deviate up the side of the valley; C = the alleviation of the impact and a return to the valley floor; D = the resumption of normal canalized growth.

on pretreatment factors, such as chronological age, height, weight, and skeletal maturity; that is, on how long the child has been deficient, how severe the deficiency in height and weight are, and by how much the maturity has been affected.

CONCLUSION

This chapter forms an introduction to the study of human growth and development. The curve of human growth has been a characteristic of *Homo sapiens* for as long as we have been walking on this earth. It has changed in duration and

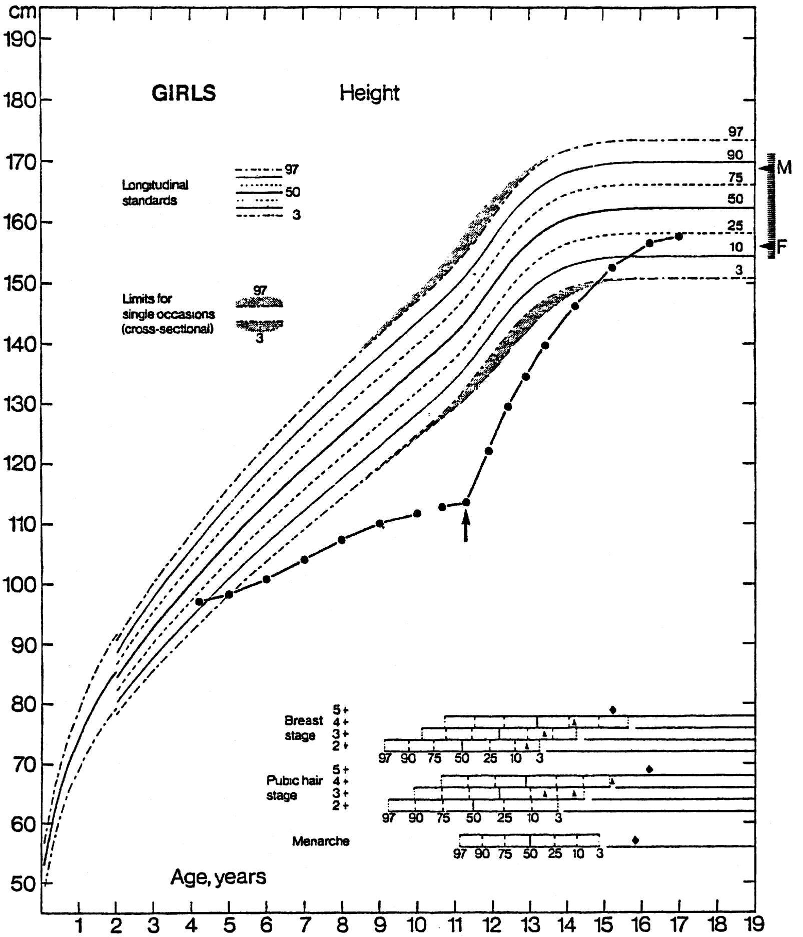

FIGURE 1-9 Catch-up growth exhibited by a child with celiac syndrome. (Data from number 102 in Tanner JM, Whitehouse RH. Atlas of Human Growth. London: Academic Press, 1980.)

magnitude as we have been freed of the environmental constraints that affected us throughout our evolution, but its major characteristics have remained unaltered. That curve reflects two major stages during which adjustment to final size and shape are the direct consequences. Infancy and adolescence are times of adjustment and assortment. More than 50% of infants exhibit either catch-up or catch-down growth during the first 2 years of life.[12] These adjustments have long-term consequences in terms of final size, shape, morbidity, and perhaps mortality. The timing of the adolescent growth spurt, its magnitude, and its duration are fundamentally important in terms of healthy and successful survival. The biological phenomena of canalization and catch-up growth dictate the magnitude, duration, and ultimate success of these alterations and adjustments.

No one would argue that environmental constraints on growth through the processes of famine and disease have been constant influences, not only on our survival but also on our size and shape at any age. Past millennia of environmental insult have resulted in the survival of representatives of the species *Homo sapiens* who are adapted and adaptable to their environment. We are the survivors and as such we use survival strategies to ensure that we continue the species. One of the most powerful of these strategies is the plasticity of our growth and development. Throughout the following chapters you will learn how that plasticity is inherited, controlled, and expressed—it is a fascinating story and one of the most fundamental biological phenomena of our species.

REFERENCES

1. http://www.ucmp.berkeley.edu/history/evolution.
2. Bloomsbury Guide to Human Thought. London: Bloomsbury Press, 1993.
3. Bourdier F. Principaux aspects de la vie et de l'oevre de Buffon. In: Heim R (ed). Buffon. Paris: Publications Françaises, 1952:15–86.
4. Tanner JM. History of the Study of Human Growth. New York: Academic Press, 1988.
5. Scammon RE. The first seriatim study of human growth. Am J Phys Anthrop. 1927;10:329–336.
6. Lampl M, Veldhuis JD, Johnson ML. Saltation and stasis: A model of human growth. Science. 1992;158:801–803.
7. Preece MA, Baines MK. A new family of mathematical models describing the human growth curve. Ann Hum Biol. 1978;5:1–24.
8. Tanner JM. Some notes on the reporting of growth data. Hum Biol. 1951;23:93–159.
9. Thompson D'AW. On Growth and Form. Cambridge: Cambridge University Press, 1917.
10. Thompson D'AW. On Growth and Form, rev. ed. Cambridge: Cambridge University Press, 1942.
11. Scammon RE. The measurement of the body in childhood. In: Harris JA, Jackson CM, Patterson DG, Scammon RE (eds). The Measurement of Man. Minneapolis: University of Minnesota Press, 1930:171–215.
12. Ong KL, Ahmed ML, Emmett PM, Preece MA, Dunger DB, Avon Longitudinal Study of Pregnancy and Childhood Study Team. Association between postnatal catch-up growth and obesity in childhood: Prospective cohort study. Brit Med J. 2000;320:967–971.
13. Tanner JM, Whitehouse RH. Human Growth and Development. London: Academic Press, 1980.
14. Waddington CH. The Strategy of the Genes. London: Allen and Unwin, 1957.

2

GROWTH IN INFANCY AND CHILDHOOD: A PEDIATRIC APPROACH

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At birth the infant is delivered into a postnatal environment characterized by extremely varied and changing conditions. He or she will be subject to intense and continuous physiological demands, which will require consequent adaptive responses during the first years of life. Growth evolving under these circumstances becomes a central subject in pediatric practice, an important objective in child health programs, a relevant health indicator, an instrument for pediatric surveillance in health centers, and an operative issue for health education in the community.

Infancy is a high velocity, rapidly decelerating, nutrition-dependent phase of growth, followed by a growth-hormone-dependent phase of growth, evolving with a slowly decelerating growth velocity during the preschool and school years. Both phases can be expressed by different mathematical functions. At birth, physical size is still strongly related to prenatal growth, and the size of the newborn may not express the size genetically determined by the parents. During the first 2 years, the genes expressing parental size become activated and some children may shift linear growth, changing centiles on distance charts, until they achieve, at around the second year, their genetically determined location on the centiles; that is, canalization.

Infancy and childhood are sensitive periods in human life. Interference with the growth process in early years may have long-term consequences for adult health. Pediatric surveillance and the promotion of normal growth in infancy and childhood includes the knowledge of its physiological basis and the skills for the selection and performance of adequate anthropometric measurements. A correct growth assessment that allows early recognition of growth alterations and identifies abnormal cases is essential for a reasonable clinical orientation of the underlying conditions.

INTRODUCTION

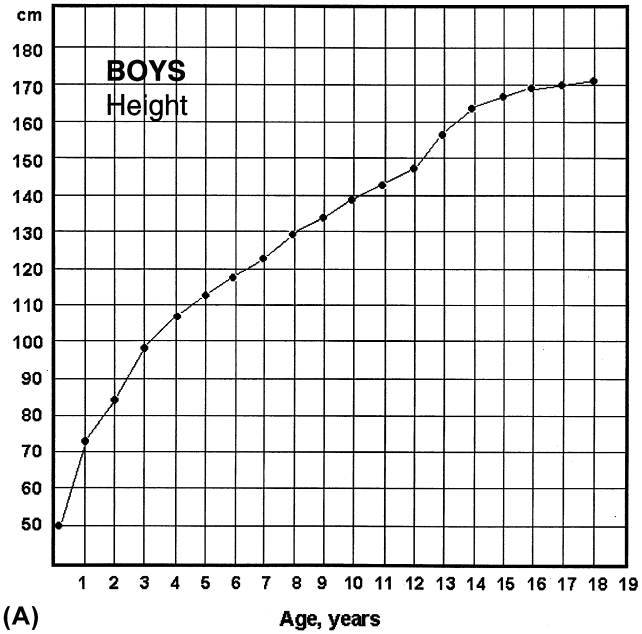
At birth, the baby leaves the uterus, where he or she lived in a protected environment with quite restricted physiological variations, and enters the postnatal environment, in which it is to develop under extremely varied and varying environmental conditions. Under these circumstances, infancy evolves under a continuous compensation to new levels of stress, "adjustment to striking environmental changes,"[1] and the continuous activation and maturation of adaptive mechanisms. Profound developmental changes in the central nervous system take place during infancy and the preschool years, providing a physiological basis for psychomotor development, including the most important intellectual adventure of the human being: the acquisition of language. During the school years and before puberty, the child acquires a large proportion of its cultural inheritance and undergoes an important part of the process of socialization. Infancy and childhood are sensitive periods in human life. Biological, psychological, and social experiences in infancy and childhood have relevant long-term consequences.

THE GROWTH CURVE

Distance and velocity curves for the height of a normal boy are shown in Figure 2-1. Other normal children would have growth curves of the same shape. They may differ in absolute height or growth velocity, the pubertal growth spurt may be experienced earlier or later, but the shape of the curve is always the same. This shape is a primate characteristic (see Chapter 14).

Infants grow very fast during the first year of life, at approximately 25 cm/yr; and during the first half of this year, velocity may be even faster, around 30 cm/yr. A rather steep and continuous deceleration can be observed form birth up to the third year. Thereafter, there is a much milder decay in velocity during school years before the adolescent growth spurt. During this period, mean peak height velocity is approximately 9.5 cm/yr in boys and 8.5 cm/yr in girls.

A small sex difference is present from birth that reaches about 1.0 cm in favor of boys by 5 years of age. The adult sex difference of 12.5–13.0 cm develops gradually prior to and during the pubertal growth spurt (see Chapter 1). For many purposes, the velocity curve can be more informative than that for distance. Three mayor phases of the growth curve can be identified: a rapidly decelerating phase, from birth to approximately 2–3 years; a slowly decelerating phase, from 3 years up to the start of the adolescent growth spurt; and the adolescent growth spurt itself. In this chapter we are concerned with the first and second phases.



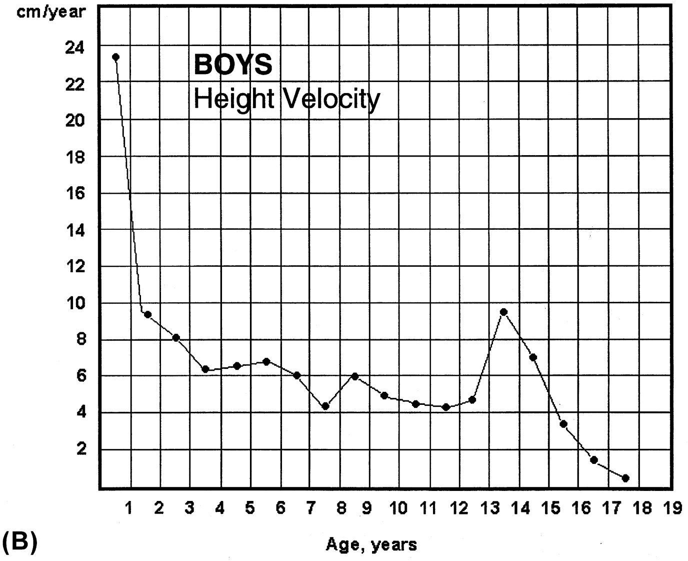


FIGURE 2-1 Distance (A) and velocity (B) curves of height of a normal boy.

INFANCY AND CHILDHOOD

A Model for Growth in Height

Although there are many mathematical ways of modeling the human growth curve, one is particularly relevant to the purpose of this chapter. Three phases of growth—infancy, childhood, and puberty—are identified and modeled by mathematical expressions. Johan Karlberg[2] designed this mathematical model, called the *infancy-childhood-puberty* (ICP) *model*. Figure 2-2 shows the decomposition of the growth curve form birth to maturity into the three parts.

The infancy component is expressed with an exponential function that describes growth as rapidly decelerating:

$$Y = a_i + b_i (1 - \exp c_c t)$$

The childhood component is a second degree polynomial function that describes height velocity as following a gradually decelerating course that continues until the end of growth:

$$Y = a_c + b_c t + c_c t^2$$

The puberty component is modeled with a logistic expression describing additional growth induced by pubertal hormones (gonadotrophins and growth hormone), which produce an acceleration up to peak height velocity and then a deceleration until the end of growth:

$$Y = a_p / \{1 + A\ [-b_p\ (t - tv)]\}$$

Karlberg's ICP model has the advantage of reflecting the main physiological features of the growth process and being compatible with their underlying endocrine and biological influences. The infancy component of the curve seems to start during fetal life, at approximately mid-gestation, and continue with a decelerating trend up to about 3–4 years. This infancy curve is strongly modulated by nutritional factors, to the point that this part of the growth curve has been called the *nutrition-dependent* phase of growth. In children with congenital hormone deficiency, height at birth and during the first year of life is not as impaired as in malnourished children. The second (childhood) component starts toward the end of the first year. After the second or third year of age, the command of growth is taken over by growth hormone, and this childhood phase is called the *growth-hormone-dependent* phase of growth. Of course, the growth hormone is not the only hormonal factor involved with growth in this phase; the thyroid hormone, insulin, cortisol, adrenal androgens, and the like also play important roles.[3] Some authors (e.g., Karlberg[2]) claimed to have seen a small spurt in growth velocity at around 2 or 3 years of age and explained this spurt as an expression of the change in command of physiological growth. In puberty, the growth spurt, with its sigmoid-shaped distance curve, is superimposed onto the childhood component and controlled by both the growth hormone and sex steroids. The development of any given phase of growth is influenced by the physiological and pathological variations of the preceding phase.

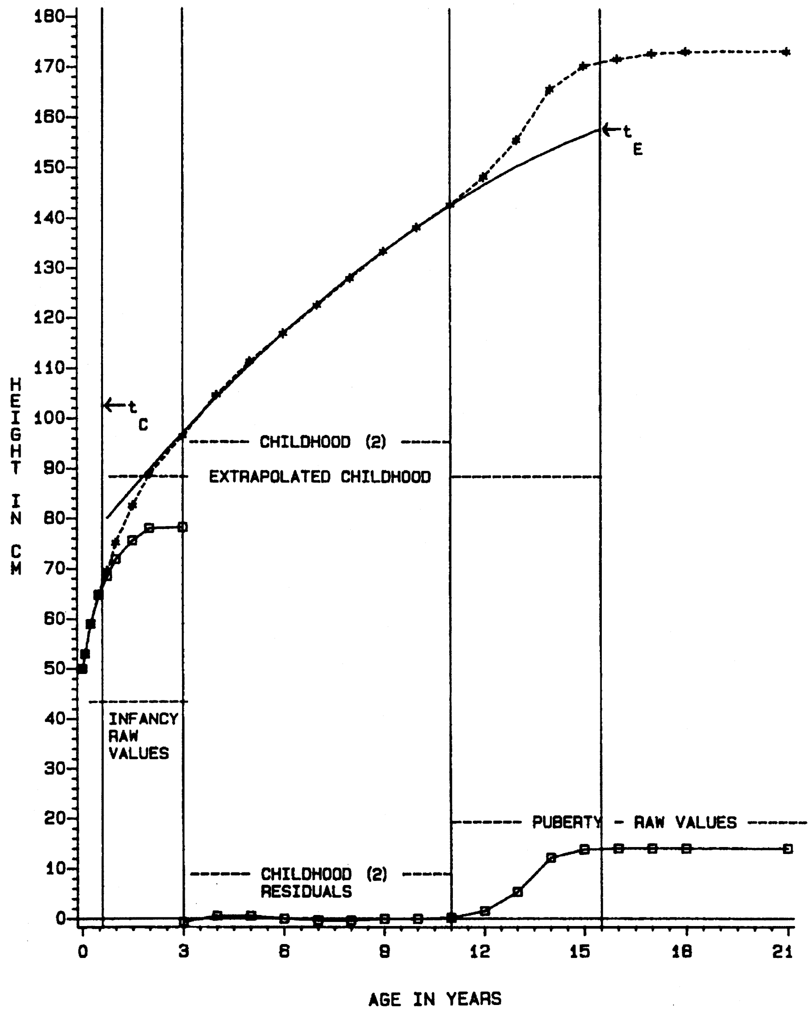


FIGURE 2-2 The three phases of postnatal growth, according to the ICP model. (Source: Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. Acta Paed Scan. 1989;350:70–94.)

This is to be borne in mind when studying growth curves in children with abnormal growth as a result of, for example, chronic disease or malnutrition.

Changes in Body Fat

Growth of fat tissue follows a completely different pattern, as shown in Figure 2-3, where growth of subcutaneous triceps skinfolds of boys and girls are plotted

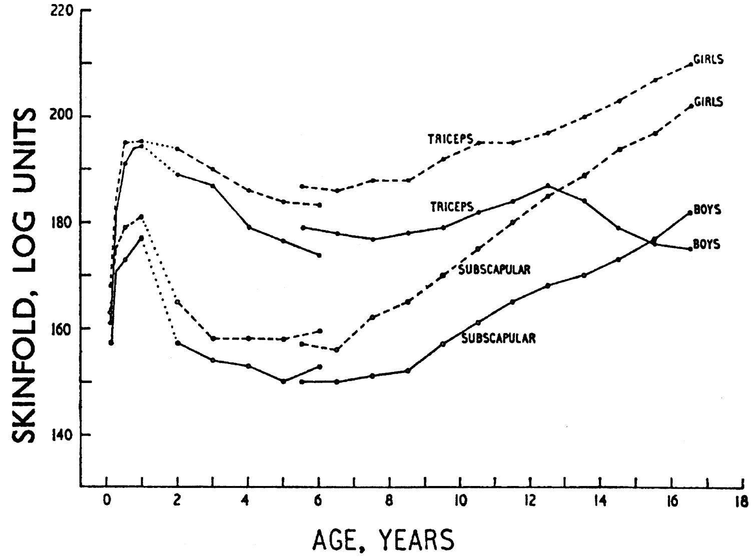


FIGURE 2-3 The 50th centile of triceps and subscapular skinfolds. (Source: Tanner J. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

against age.[4] The slopes of the curve at different ages are similar to those expressed by the growth of total body fat (see Chapter 13). Fat tissue exhibits an important increase during the first 9 months of postnatal life. The baby is born with a relatively small amount of body fat, about 14%, which rapidly increases to about 25% by 6 months and stays at this level throughout infancy but has decreased to about 15% by 5 years. After birth, the infant is thus equipped with an energy reserve that helps it cope with one of the most dangerous periods for nutrition scarcity in human evolution, weaning. After the first 6 months of postnatal life, breast milk does not fulfill the increasing nutritional needs of the infant. Therefore, weaning is initiated, and from an evolutionary perspective, the infant enters into competition with other human groups and other species for appropriate food sources.

Weaning should not be considered a single event, as it is actually a process of gradual incorporation of new, "solid" foods into the diet from approximately the age of 6 months. Initially, this complements breast milk, but after several months it replaces it. The process involves the activation of a multiplicity of what could be called *family functions*. These include the acquisition and selection of adequate food (not only in quantity but in quality), the development of certain food preparation and presentation technologies, the development of psychomotor skills in the baby to enable it to eat, changes in family routines, and so on. When these functions are not met or in areas of food scarcity where these functions break down, there is a high risk of growth delay during the weaning process. Growth during the weaning period should be specially surveyed in pediatric programs.

The second year of life coincides with a decline in skinfold thickness, and the baby changes its initial plump "babylike" appearance toward a leaner, slender body build. This is a period coincident with important progress in psychomotor skills: The child is now able to walk and run and develops an extraordinary amount of physical activity and energy expenditure. During childhood (5–10 years old), the percentage body fat remains quite stable, as do many other growth indicators, to the extent that childhood growth velocity has been characterized as a plateau, reflecting a quite stable period of somatic growth. Body fat continues to be greater in girls than boys, a genetic difference that holds true in skinfold thickness and percentage of total body fat. By 5 years old, the sex difference is about 2% (14.6% for boys and 16.7% for girls) but this difference increases to almost 6% by 10 years old.

SOME PARTICULAR FEATURES OF GROWTH DURING INFANCY AND CHILDHOOD

Parental Size and Size at Birth

Growth is the result of three forces: the genetic program, the action of environmental factors, and the interaction between the two. One simple example of the influence of genetics on physical growth is that tall parents tend to have tall children and short parents tend to have short children. The relationship between the height of children and their parents is a useful tool for growth assessment, especially in childhood and puberty. However, in the first 2 years of postnatal life, this relationship is not as close as at later ages. Physical size during the first 2 years of life is related more to prenatal growth than the size of parents, and in turn, prenatal growth cannot be solely explained in terms of the genotype of the fetus.

Figure 2-4 shows the correlation coefficients between the height of the child as an adult and the height of the same child at each age from birth onward.[5] Size at birth is poorly correlated with adult size; the values rise steeply during the first 2 years to a level of about 0.80, then become quite stable with very small variations until adulthood. The single major variation during adolescence is due to differing rates of maturation (see Chapter 3). This means that not all genes regulating body size are fully expressed at birth. After birth, they gradually become more influential, until they can express their full influence after the age of 2 years. This is not the only example showing that some genes have a particular period of time in which they are active. At other times, they are either inactive or their effect is masked by other (environmental) factors. In the case of infants, their size in the first 2 years of postnatal life at a given age is related more to size at birth (and, consequently, to fetal growth) than the height of parents. The knowledge of those factors regulating fetal growth is then crucial for evaluating growth in infancy.

One of the factors proven to be very important in the modulation of fetal growth is maternal size. Small mothers tend to have small babies, and large mothers tend to have large babies, independent of their genotype. A very illustrative experiment

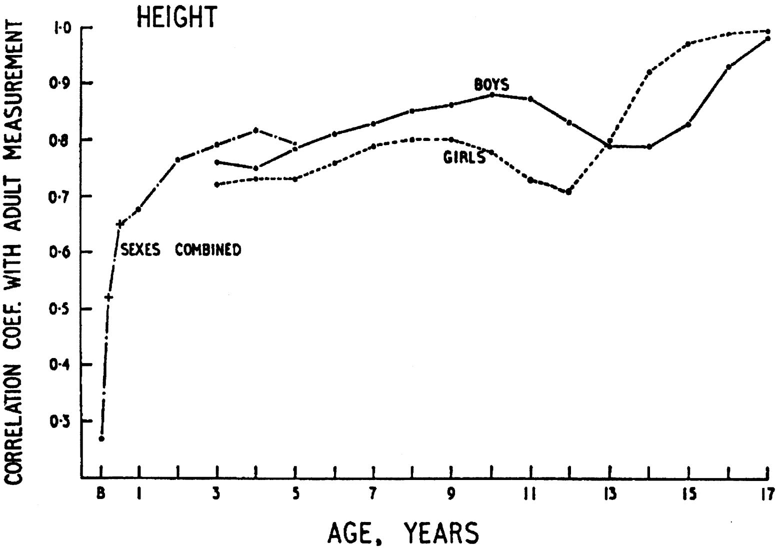


FIGURE 2-4 Correlations between adult height and height of the same individuals as children. (Source: Tanner J. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

was carried out in the 1930s by Sir John Hammond at Cambridge University.[6] Using artificial insemination techniques, this research group crossed a Shetland pony mare with a Shire horse sire, and a Shire horse mare with a Shetland pony sire. Birthweights of the foals were in accordance with maternal size. The offspring of the large mother had a greater birth weight than that of the small mother, even though both offspring shared the same proportion of genes from each parent. This action is not gene mediated, and many studies of the relationship between size of the child at different ages and size of parents confirm this statement. This is an adaptive mechanism from the evolutionary point of view: It allows a genetically large fetus to be delivered by a small mother, with less risk of having a dangerous labor due to a large fetal size at birth.

The clinical importance of this phenomenon is that the size (but not growth rate) of babies in the first months of life is related more to their experiences during prenatal life than the height of their parents. Therefore, in a clinical assessment situation, we should not adjust an infant's height to the height of parents during the first years of life. When presented with a small baby, we should obtain information on its fetal growth, maternal health, maternal weight increment during pregnancy, drug intake, nutrition, and so forth. This information may greatly contribute to the understanding of the problem of small size of the patient during infancy.

Shifting Linear Growth During Infancy: An Example of Catch-up and Catch-down Growth

This observation is, to a certain extent, a direct consequence of the former concept. If phenotypically small babies can be born to genetically large parents and phenotypically large babies born to genetically small parents, then most of these children at some age must seek their respective centile related to their genetic size: They must acquire a canalized pattern of growth. If this is true, a considerable proportion of children must shift centile lines during the first 2 years of age. David Smith, an American professor of Pediatrics, confirmed this hypothesis in 1976.[7] He found that approximately two thirds of normal infants shifted centiles upward or downward, achieving a new growth canal by 11–13 months of age. This means that, during the first 2 years of life, not all deviations of growth curves from the centile lines are necessarily abnormal. Size at birth of the child and parental size may help distinguish between normal and abnormal shifts. Velocity charts for weight increments in short periods of observation may also help (see later).

The process of shifting linear growth during infancy is an example of the catch-up or catch-down growth that results in canalization. Catch-up and catch-down growth during infancy are special examples of the response of the child to the physical environment of the uterus. The former is in response to the constraining effect of a genetically large mother with a small uterus and the latter is in response to a genetically small mother with a large uterus.[8,9]

Mid-Childhood or Juvenile Growth Spurt

The plateau in growth velocity occurring between 5 and 10 years of age is interrupted between 6 and 8 years in both sexes by a growth spurt called the *mid-growth* or *juvenile growth spurt*. Although some authors claim that this spurt is present only in boys, others have found it to occur in both sexes at similar ages and magnitudes.[10–12] This spurt is relatively small in linear dimensions, such as height, but is larger and more pronounced in dimensions relating to volume such as weight or skinfolds.

Figure 2-5, from the work of James Tanner and Noël Cameron on children in London, illustrates clear mid-growth spurts in calf circumference velocity in both boys and girls.[12] Note that, although there is only a minor sex difference in the timing but not the magnitude of the mid-growth spurt, the subsequent adolescent growth spurt exhibits the usual enhanced sex difference, with boys being relatively delayed. Research by Swiss investigators has confirmed that the absence of sex differences in the mid-growth spurt and also that this spurt is uncorrelated with the timing or magnitude of the adolescent growth spurt, except that it occurs closer to adolescent growth spurt of the girls than the boys. The mid-growth spurt has been attributed to adrenarche characterized by an increase of the secretion of androgenic hormones of adrenal origin (see Chapter 5). This phenomenon coincides also with the appearance of axillary and pubic hair, secondary traits to those hormones.

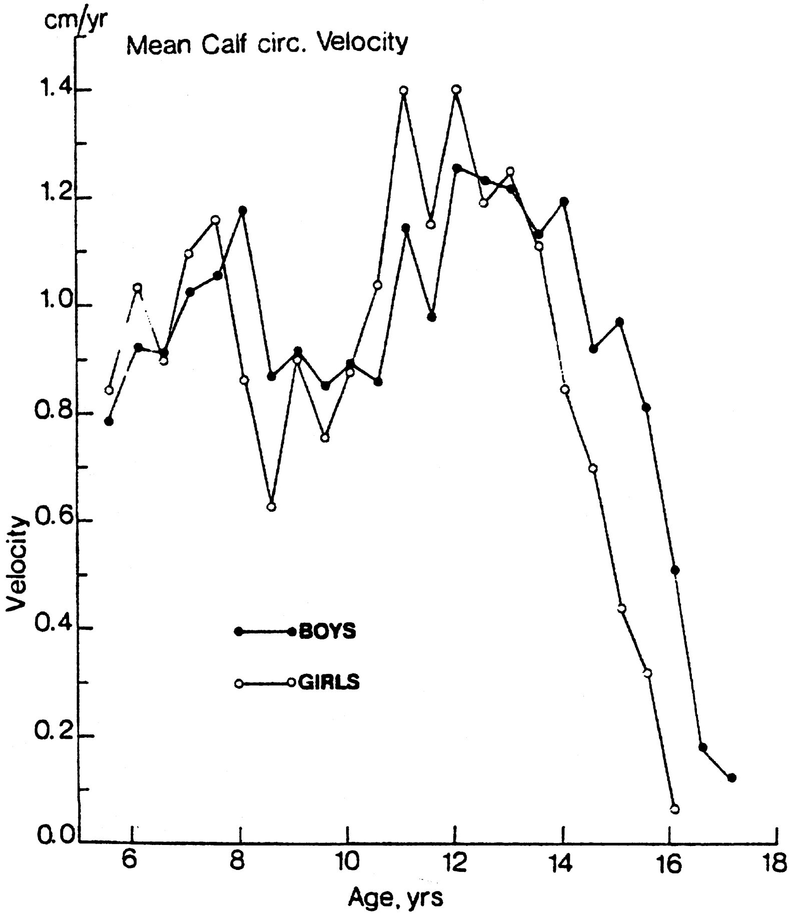


FIGURE 2-5 The mid-growth spurt in calf circumference velocity in London children. (Source: Tanner JM, Cameron N. Investigation of the mid-growth spurt in height, weight and limb circumferences in single-year velocity data from the London 1966–67 growth survey. Ann Hum Biol. 1980;7:565–577.)

THE RELEVANCE OF PHYSICAL GROWTH TO PEDIATRICS

Physical growth is an issue of paramount importance in pediatric practice. It is a central objective in child health programs, because the ultimate goals of such programs are not simply to reduce infant mortality but to provide the health care and environmental conditions to allow children to grow and develop normally to achieve their genetic potential as healthy adults.

Growth is also an *instrument*, for one of the most relevant actions to be taken in programs of child health surveillance is monitoring physical growth. It is also an excellent *indicator* of general child health and nutritional status. Some conditions can be recognized because the first clinical sign is growth delay, as sometimes happens with malnutrition, acquired hypothyroidism, and celiac disease. Hence, growth can be the first sign of an underlying disease in otherwise normal, asymptomatic children. One of the main general indicators and criteria of success used for the treatment and surveillance of chronic diseases is physical growth. Growth is also used in some cases to evaluate important therapeutic decisions in the surgical treatment of some conditions. For example, in some cases of surgical correction of gastroesophageal problems, physical growth of the operated child is an important indicator of success. Some drug treatments, such a steroids or immunosuppressing agents, used in chronic diseases can affect physical growth; and their therapeutic benefits should be constantly balanced against their impact on growth and, of course, other secondary effects.

Physical growth is a relevant subject and a highly motivating issue for the parents; it enhances the communication among them, the pediatrician, and the rest of the health personnel, being an excellent central subject for the articulation of programs for health education to health professionals and to the community. All centers where children receive medical care should be provided with the appropriate personnel, anthropometric instruments, and growth charts for the proper assessment of physical growth in children.

Measurements of Clinical Importance

The three most important anthropometric measurements to be taken in pediatric practice are height, weight, and head circumference. These measure different components of the body, and their changes have different clinical and biological meaning.

Height

Height is a linear, unidimensional measurement. Although it mainly indicates the length of long bones of the lower limb (tibia, femur) and the irregular bones of the vertebral column, it is also an indirect indicator of the growth of the total lean body mass. In clinical pediatrics, changes in growth of height need a rather long period of observation to be detected (3 months or more), depending on the precision of the measurements. When growth in height is impaired, it can be assumed that an important health problem is present.

Weight

Weight is a three-dimensional measurement that includes both lean body mass and body fat. The relative proportions and distributions of lean and fat components depend on age, sex, and other environmental and genetic factors. Weight is a very sensitive measurement, in the sense that it can change from one day to another due to very minor alterations of body composition, for example, the changes seen in infants during a common cold. A change in weight does not tell us which particular tissue is being affected. Changes in body weight can be secondary to changes in body water (dehydration, overhydration), muscle mass (muscle hypertrophy by training, muscle atrophy), total lean body mass (wasting), fat (obesity, malnutrition), and so on. Weight changes can also be secondary to changes in body height, as it happens in growth retardation in stature or stunting.

Weight-Height Ratios

Some children have a low weight, not because they are lean but because they are very short, while others are heavy, not because they are obese but because they are very tall. This is a limitation to consider when we want to evaluate the amount of body fat as an indicator in nutritional assessment. One way to evaluate body fatness directly is by measuring subcutaneous fat using skinfolds. A way to do it indirectly is to evaluate weight in relation to height. A number of weight-height ratios exist, which use different power values. That most commonly used in pediatric practice is Quetelet's index, more commonly known as the *body mass index* (BMI). BMI is calculated from the formula BMI = weight/height^2, where weight is in kilograms and height^2 is in meters squared. Cutoff values for BMI describe obesity in both children and adults (see Chapter 18). In adulthood, a BMI greater than 25 kg/m^2 is indicative of "overweight" and greater than 30 kg/m^2 is indicative of "obesity." Childhood BMIs are much smaller than adult BMIs. The British BMI centiles developed by Cole, Freeman, and Preece[13] show that BMI in childhood increases rapidly in the first year to peak at a 50th centile value of about 18 kg/m^2. Deceleration follows until about 6 years of age, and then there is a steady increase until adulthood. The 50th centile BMIs in childhood (2–11 years of age) are less than 17 kg/m^2 and during adolescence rise from 17 kg/m^2 to about 22 kg/m^2. BMI cutoffs for obesity, set at the 98th centile, are at a minimum of 18.5 kg/m^2 at 5 years of age and then climb to 29 kg/m^2 at 20 years of age. In addition to identifying overweight and obesity, BMI is also used to identify "wasting" or a low weight for height. Wasting is prevalent in developing countries where acute nutritional deprivation is registered by a lowered weight in relation to height.[14,15]

Head Circumference

Head circumference is the expression of growth of the brain; and its measurement is very important, especially during the first months of life, when it may be used to detect excess growth due to hydrocephaly. Congenital microcephaly can also be easily detected in infancy by measuring head circumference. Because of the rapid growth of the brain, head circumference increases relatively faster than height and weight in early years. At any given age, the brain is nearer its adult size than height and weight. At the age of 2 years, the brain, and therefore head circumference, have achieved nearly 80% their adult size, whereas height and weight have achieved only 50% the adult size. Because of this early rapid growth, head circumference is more liable to be affected by malnutrition or disease in the early years. Therefore, its importance for evaluating nutritional status in later childhood is diminished and seldom used on school-age samples.

These measurements should be performed in pediatric health centers with an adequate frequency, although it may vary according to available local resources. Weight and head circumference are recommended to be measured monthly during the first months of life, supine length should be measured every 3 months in this period. They can later be progressively spaced. Longitudinal studies of growth tend to be measured at 3-month intervals in the first 2 years, 6-month intervals to the start of adolescence, and every 3 months thereafter until adulthood (see Chapter 16).

GROWTH PROBLEMS IN INFANCY AND CHILDHOOD

Defining the Auxological Diagnosis

One of the most common causes of pitfalls in pediatric practice concerning the study of growth problems is the ambiguity in initially defining a growth problem. Failure in defining whether a child is too short, too light, or not growing at a normal velocity may be misleading with regard to further actions. The parents are usually very unspecific in stating the problem: They may say, "This child does not grow" when, in fact, they mean, "The child is too short" or "too light." These diagnoses are essentially different and have different clinical meaning.

In practice, when the clinician sees a child with an apparent growth problem he or she should ask two main questions:

1. Is this child's size normal for his or her age?
2. Is this child growing at a normal velocity for his or her age?

To answer the first question, the child should be appropriately measured and his or her height and weight plotted on appropriate *distance* charts, such as the one shown in Figure 2-6 for Argentinean children.[16]

The relative merits of international as opposed to national growth charts have been discussed on numerous occasions (see Chapter 18). The general consensus of opinion is that national charts, based on a selected sample of well-off children who have not been exposed to constraints on their growth, are appropriate as "standards" to reflect growth as it should be in the best possible circumstances within the chosen national environment (Figure 2-7). They are thus appropriate for the clinical monitoring of individual children. Currently available "reference charts" for international use include children from a variety of backgrounds and should be used to compare mean values for groups of children.[17] If the height (or weight) falls within the centile lines, the child is classified as having a normal height or weight. The lower limit is generally set at the third centile, but this is a convention. The setting of a normal limit implies the assumption of a given sensitivity and specificity. Sensitivity is the power of detecting pathological cases; specificity is the power of recognizing normal cases. If we want a limit with a sensitivity greater than the third centile, we should then set the limit at an upper centile, for example,

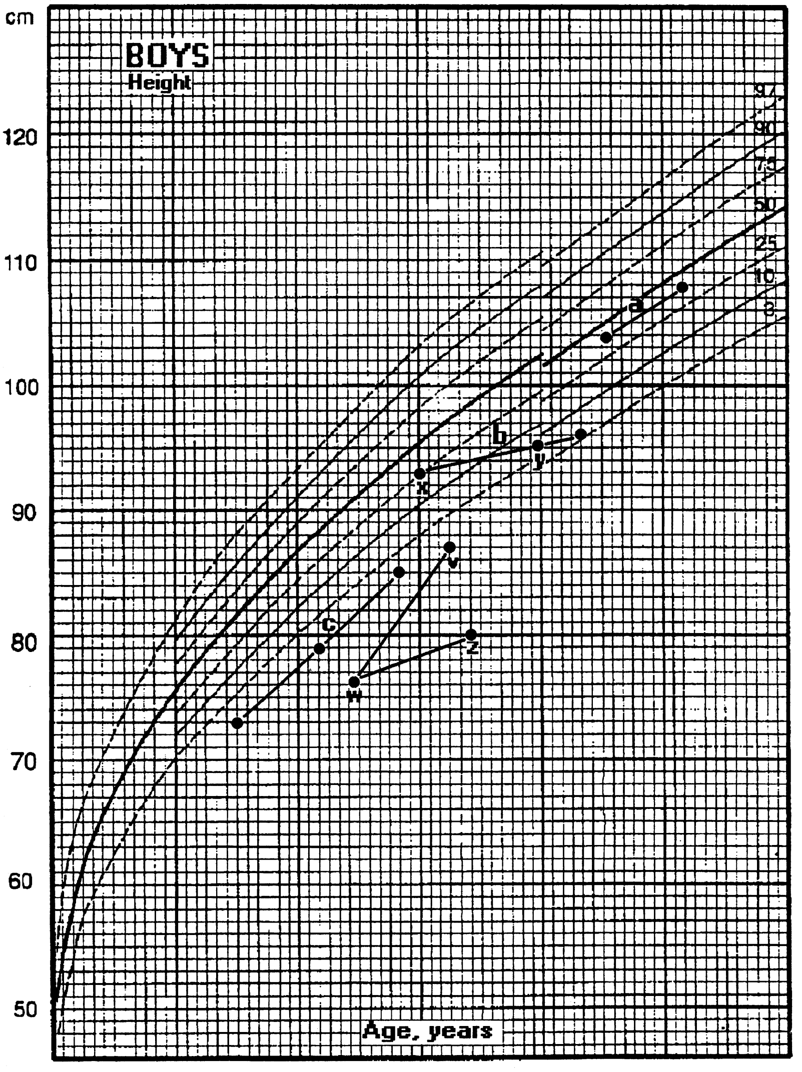


FIGURE 2-6 Argentine standard for height attained in boys. (Source: Lejarraga H, Orfila G. Estandares de peso y estatura para niñas y niños argentinos desde el nacimiento hasta la madurez. Arch Argent Ped. 1987;85:209–222.)

the 10th centile. But this will be at the expense of reducing specificity. If, on the contrary, we want to increase specificity, then we should set a limit below the third centile, say at the first centile, but this, in turn, implies a reduction in sensitivity.

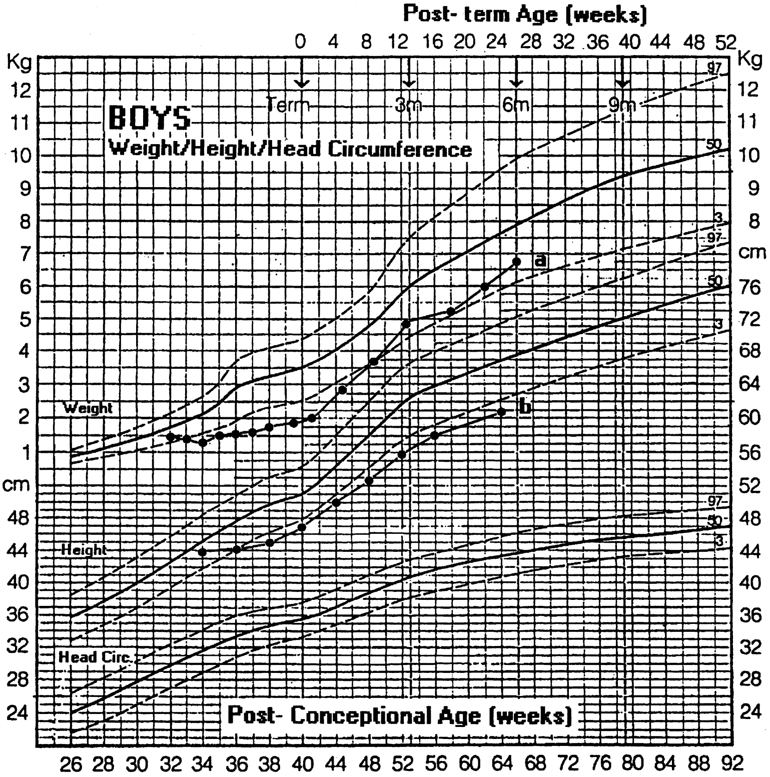


FIGURE 2-7 Argentine standard for weight, height, and head circumference from 26 to 92 weeks of postconceptional age. (Source: Lejarraga H, Fustiñana C. Estandares de peso, longitud corporal y perímetro cefálico desde las 26 hasta las 92 semanas de edad postmenstrual. Arch Argent Ped. 1986;84:210–214.)

In clinical pediatrics, the third centile is commonly used. If this limit is chosen, then bear in mind that 3% of normal children would fall below the third centile line. Many of these children, for social or psychological reasons, may go to the doctor complaining of short stature. Hence, the majority of children complaining of short stature will belong to this group of entirely normal individuals.

To answer the second question, we need at least two measurements separated by an appropriate period of time, in order to calculate the growth velocity during the period between measurements. In Chapter 16, the way growth velocity is to be calculated and evaluated on velocity charts is explained in detail. Velocity charts tell us whether the child is growing too fast, too slow, or at a normal velocity. Growth velocity can be indirectly estimated on distance charts. Let us suppose we have a patient measuring 104.0 cm at the age of 4.5 years, falling on the 35th centile of

Figure 2-6. To determine his growth velocity, we measure him a second time at the age of 5.2 years, obtaining a height of 109.0 cm. If the slope of the growth curve created by joining both points with a line is parallel to the centile lines (curve *a*, Figure 2-6), we can assume that growth velocity is normal. On the other hand, if the slope of the distance curve falls away from the centile lines, as in curve b, then we must say that the child is growing too slowly. This condition should be specified as growth retardation, growth delay, or abnormally slow growth.

In young infants, with whom we cannot wait a long period of time to evaluate growth velocity in height or we have doubts on the slope of the weight curve in the first months of life, it has been very useful in our growth clinic to evaluate velocity in terms of daily weight gain in grams/day. For example, if a 3-month-old infant is seen in the clinic on January 16 weighing 6700 g, and she comes for the second time on February 24 (39 days later) weighing 6950 g, then her growth velocity (GV = the change in distance divided by the change in time) is GV = (6950 g – 6700 g)/39 = 6.4 g/day, which in Figure 2-8 falls well below the 10th centile line of normal values for weight velocity.[18] This method also allows for children attending the clinic at very irregular intervals.

As we can see in Figure 2-6, size attained and growth velocity are both rather independent concepts. Some cases show normal size (example b) growing at a slow velocity (from *x* to *y*), other cases show short stature (example c) growing at a normal rate, and in still others, both size attained and velocity are abnormally low (from *w* to *z*). Size attained can be considered the cross section of a continuous growth process taken place from birth (or better, from conception) up to the moment in which the child was measured. It is the result of the algebraic sum of all growth experienced before the measurement was taken. Growth velocity, in turn, reflects the process occurring exclusively during the period in which the child was measured.

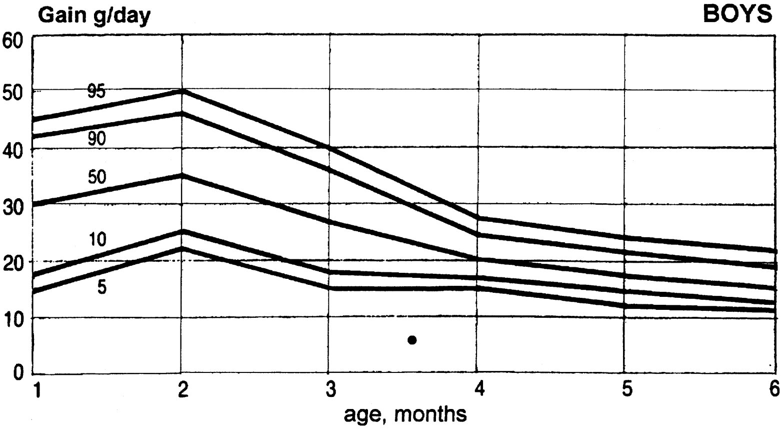


FIGURE 2-8 Centiles of daily weight increments of normal infants. (Source: Drawn from data in Roche SG, Fomon S. Reference data on gains in weight and length during the first two years of life. J Ped. 1991;119:355–362.)

A short child may or may not be ill at the time of measurement: He may have a late sequelae from a process occurred in the past. On the contrary, if a child is not growing at a normal rate, then we are certainly facing a pathological condition, occurring during the period in which she was measured. Growth velocity provides excellent information of the dynamic condition of the growth process. For example, Figure 2-6 (point *c*) shows the attained height of a malnourished child 2 years old. We can say there is a marked height deficit. If the following measurement was point *z*, it would mean that the growth rate is abnormally slow and the child is progressively deteriorating and at high risk. On the contrary, if the following measurement was point *v*, then growth rate is higher than normal and we can assume the child is in the process of catching up and recovering from malnutrition.

Some Considerations of Pediatric Value

Both growth delay or small size are quite common causes for consultation in pediatric practice. However, they are unspecific clinical signs, because growth impairment may have a great variety of underlying causes. The majority of the causes of growth problems at the primary care level can be identified without the use of sophisticated tests or studies.

In general, the clinical approach to growth problems in the first 1 or 2 years of life should be a different approach than to growth problems appearing later. In the first year of life, small size or short stature frequently is related to the pre- or perinatal period. In other cases, especially growth delay during the first year, they are secondary to causes of multifactorial origin. In case of growth delay in the school years, if the child is asymptomatic, we can take more time to search for the underlying cause. For example, we could evaluate the growth velocity over a period of 6 or 12 months without seriously affecting the prognosis. However, if the patient is an infant, we cannot wait such a long time. Growth problems presenting during infancy should be investigated and diagnosed as early as possible.

The long-term consequences of growth delay in infancy may be serious. The obvious result of growth retardation during this period of life is short stature. The risk of the final height being adversely affected as a consequence of growth delay is higher if the delay takes place during infancy, because the child is growing very quickly at this time. There are also other possible consequences of early growth delay. Martorell et al.[19] have described educational and functional impairment in adulthood as a result of stunting at 3 years of age in a sample of impoverished Guatemalan children. Studies carried out in the United Kingdom in the last 20 years suggest that growth retardation during prenatal life and the first year of postnatal life may be associated with a variety of adult conditions including cardiovascular disease, stroke, hypertension, non-insulin-dependent diabetes mellitus, and low bone mineral density. The mechanisms underlying this association may be related to early metabolic changes in hormone interactions and modalities of tissue responses to these hormones, with persisting and long-term consequences in adult life. This phenomena of early metabolic changes being associated with late consequences are referred to as *fetal* or *metabolic programming*.[20–22]

In childhood, growth problems have an important impact on the child's psychosocial adjustment. The problem itself, and the accompanying clinical and laboratory studies directed to the identification of the problem, may interfere with school performance, sports, and social integration.

As happens in other phases of growth,[9] the chance of experiencing complete catch-up depends on the duration of the factors causing growth delay, their intensity, the age at which they occur, and as stated by McCance, the "individual thrive to grow."[23]

Causes of Short Stature

The description of the causes of short stature varies according to the auxological diagnosis. If we want to describe causes of small size (weight or length), the picture is different to the description of the causes of growth delay. Taking into account that, in a clinical setting, this problem is usually presented as smallness, we describe causes of short stature defined as height below the third centile of appropriate height-for-age (distance) charts.

Malformations, Deformations, or Alteration of Body Proportions

In these cases, short stature is only a part of the clinical picture. This group includes children with skeletal dysplasias, some of neonatal onset (e.g., achondroplasia), some others detected after the second year of life or even later in childhood (e.g., hypochondroplasia, dyschondrosteosis); dysmorphic syndromes, either of genetic origin (e.g., Noonan's syndrome), chromosomal alterations (e.g., Turner's syndrome), or due to prenatal infections (e.g., congenital rubella syndrome); and teratogenic malformations (e.g., fetal hydantoin syndrome, fetal alcohol syndrome). Some syndromes evolve with a normal growth velocity in childhood, such as Silver-Russell syndrome, but others with a slow growth velocity, such as Turner's syndrome.

Dysmorphic syndromes and chromosomal disorders are well described in books specially dedicated to their clinical identification.[24] Searching devices built on information databases may be helpful in the diagnosis.[25] Some syndromes are quite frequent (for example, Turner's syndrome has an incidence of 1 in every 2500 female births), and others are rarer, such as achondroplasia (one case in every 26,000 births), see Chapters 10 and 11.

In the Absence of Dysmorphism, with Normal Body Proportions

Extreme Variations of Normality

Extreme variation of normality includes two conditions: familial short stature and delayed maturation. Both are normal conditions and the most frequent diagnosis made in clinical practice.

A diagnosis of familial short stature (FSS) is made in normal children older than 2 years, with no underlying disease, normal physical examination, and normal growth velocity. Height is usually within –2.0 and –3.0 SD (standard deviation) scores, or *Z*-scores, and the height of the child adjusted to that of the parents is within normal limits (–2.0 and +2.0 *Z*-scores). The parental adjustment can be calculated by subtracting the average of the parents *Z*-scores from the child's *Z*-score. For example, in a child whose height *Z*-score is –2.5 (less than the third centile and perhaps indicative of abnormal short stature), the father's height is –0.98 *Z*-score and the mother's height is –1.66 *Z*-score, the child's adjusted *Z*-score for height (AHZ) is AHZ = –2.50 – {[(–0.98) + (–1.66)]/2} = –1.18 SD, which is within normal limits.

Much care should be taken, however, when a parent's height is below normal limits for population standards, for the parent may have a pathological condition and, in turn, this condition may have been inherited by the child. Also, when the child's height deficit is below –3.00 *Z*-scores, the diagnosis of FSS should be put in doubt. In FSS, predicted final height using the most common methods[26] is within the genetical range. This range (10th and 90th centiles) is within ±7.5 cm of the corrected mid-parental height. Mid-parental height is "corrected" for the sex of the child under consideration by adding 13 cm to the height of the mother if the child is a boy or subtracting 13 cm from the height of the father if the child is a girl (13 cm is used because this is the average difference in adult stature between the sexes). If both mother and son were on the 50th centile (0 *Z*-score) as adults, we would expect the son to be 13 cm taller than his mother. A 50th centile daughter would be expected to be 13 cm smaller than her 50th centile father. For example, for a boy, whose father and mother's heights are 167.0 and 158.0 cm, respectively, the genetic range is [167.0 + (158.0 + 13)]/2 = 169.0 ± 7.5 cm. The height of the parents should be actually measured in the clinic, since parental height by hearsay has proven to be quite unreliable,[27] and consequently, the estimated genetic range is expected to be wider.

A diagnosis of delayed maturation is made in children with late onset of puberty, delayed skeletal maturation, or both with no other abnormal feature and normal height velocity. Both conditions usually are present but not always, since bone age does not correlate well with pubertal events with the exception of menarcheal age. There is usually a family history of delayed puberty that is more evident by a mother's late menarcheal age than by evidence from the father. Predicted height is within the normal parental height, however, it is very common that, during puberty, the acceleration of bone age is below the predicted one. On average, children with delayed maturation attain a height some distance below their genetic target. Physical examination is normal, and growth velocity is also normal during childhood. This diagnosis is more frequently made in boys than in girls, which may be a reflection of problems in self-esteem and psychosocial integration, especially in puberty.

Perinatal Problems

Intrauterine growth retardation (IUGR)[28] is diagnosed when the weight or length at birth is low for the infant's gestational age. Birth length is related more to the height the child attains in childhood or at maturity, whereas birth weight is strongly related to neonatal mortality and morbidity. A proportion of children who have growth retardation catch up in postnatal life, either during the first years or even during childhood. Approximately 20% of all IUGR children do not catch up at all.

The possibility of catching up depends on the type or nature of the IUGR experienced in prenatal life, including the nature of the damaging agent, its timing of occurrence, and duration. If the impairment took place in the first trimester, as happens in congenital rubella, then the probability of catching up is almost nonexistent, and at school age, the child will have the same growth deficit as at birth.[29] In the case of mild growth impairment experienced in the last trimester, as happens with many cases of twin pregnancy or minor diseases of short duration suffered by the mother, then catch up is feasible, and it is usually detected in the first few postnatal months. In between these two extreme situations are many intermediate conditions.

Preterm babies born with normal weight for their gestational age can also be small during the first year of life, but due to a different mechanism;[30] growth delay after birth. The growth assessment of preterm babies should include the use of a chart that allows for an age calculation based on gestational age. Figure 2-7 shows an example of such chart, where the *X*-axis indicates the age, in terms of postconception age.[31] This is calculated counting the time in completed weeks elapsed from the first day of the last menstrual period up to the day of birth. The menstrual period is an indicator of the time of conception, which is why this age is called the *postconception age*. This age is marked in the chart until 92 weeks, exactly 1 year after term (i.e., 40 weeks of full-term gestation plus 52 postnatal weeks).

Curve *a* of Figure 2-7 shows the postnatal growth of a baby born at 32 weeks gestation with a birth weight of 1200 g. This birth weight is located on the 25th centile, hence, the child has an adequate weight for gestational age. This baby spent 3 months in an incubator, during which time he had many complications (feeding, respiratory, and metabolic problems). His growth curve could not be kept within the centile lines in which he was born, and his growth rate was slower than normal during the period 28–41 weeks postconception. Afterward, when he became easier to feed, he started recovering weight and finally experienced a complete catch-up growth. In this baby (as in many others), three phases of growth can be identified:[32] the first period with a growth retardation, followed by a second period of catch-up, and then a third period with a normal growth rate. Not all preterm babies grow this way. Some of them, like curve *b*, may not catch-up and remain with a height deficit during the rest of their infancy and childhood. These children may present at later ages for short stature. Their clinical examination and growth velocity at later ages is normal, and unless a careful perinatal history is taken, the cause of their short stature may remain obscure.

Immediate postnatal growth of newborn groups in institutions is a good indicator of the quality of perinatal care, and in my view, standard and comparable ways of evaluating it should be developed as positive indicators of perinatal care and as an important complement to neonatal mortality.

Malnutrition

Primary malnutrition is consequence of reduced nutritional intake (either predominantly proteins, predominantly calories, or both), strongly associated with unfavorable socioeconomic conditions. Kwashiorkor (predominantly protein deficiency) and marasmus (predominantly calorie deficiency) are perhaps the most frequent causes of growth impairment in the world. They are frequently observed in developing countries[33] and in inner cities and marginal groups of developed countries. The severity of the growth deficiency is proportional to the severity of the nutritional deficit.

Depending on the duration and quality of protein and energy deficiency and the relative impact on growth in weight and height, two main types of malnutrition can be recognized: stunting and wasting.[34] Wasting, assessed by the weight-for-height index, is the expression of present nutritional state and near past food intake; it is also associated with a high risk of disease and death. Stunting, assessed by the height-for-age index, is an indicator of past nutrition. It is not necessarily associated with a higher risk of disease and death.

Recent research has suggested that body composition in late childhood may be associated with the relative intake of energy and proteins in early life. A high-protein/low-energy intake in infancy is associated to a higher degree of fatness in late childhood. This association may in turn be related to the influence of the early diet on hormone secretion.[35]

Psychosocial Deprivation

Type 1 psychosocial deprivation (PD) applies to infants with nonorganic failure to thrive. Maternal deprivation, lack of adequate nutrition, and other factors may intervene in this entity, in combination with deficit in the swallowing function, deficiency of micronutrients, and the like. There may be reduced growth velocity in weight, height, or both. Type 2 PD applies to children older than 3–4 years of age, in whom nutritional deficiencies are not apparent, and the underlying mechanism is thought to be growth hormone deficiency.[3]

Chronic Disease

Practically any chronic disease may have an impact on physical growth. The most frequent entities seen in practice are severe asthma, malabsorption (e.g., celiac disease, chronic inflammatory disease, cystic fibrosis), congenital heart disease (especially with right to left shunt or cardiac failure), chronic renal failure, chronic anemia, metabolic acidosis of any origin, chronic pulmonary disease, and chronic infections (e.g., tuberculosis, AIDS). The mechanisms underlying growth delay in these entities are varied, such as reduced nutritional intake (secondary to anorexia, malabsorption, volume-limited intake), metabolic disbalance, hypoxia, chronic metabolic acidosis protein loss, and not infrequently, the treatment itself.

With the progress of therapeutic resources in medicine and the consequent reduction in mortality, the impact of the chronic disease on growth is becoming more and more important. From the point of view of the health care team, this becomes an indicator of treatment quality, and from the patient's point of view, an indicator of quality of life. In the case of acute lymphoid leukemia, for example, currently more than 90% of children survive after 8 years of treatment. After this and many other important advancements achieved in the last years, we could say, "children do not die anymore, but . . . how do they grow?" There is thus a new challenge for the clinical management of children surviving diseases that were lethal in the near past.[36]

Treatment

Some drugs are well known for their negative impact on growth. A major one is adrenal steroids, widely used in asthma, nephrotic syndrome, lupus, and many other chronic diseases. Any dose greater than the physiological one may delay growth, and the magnitude of the retardation is proportional to the dose and the duration of the treatment. Doctors know that sometimes a high price is paid for achieving a successful treatment, and in these cases, a continuous balance between the need to maintain the patient in an asymptomatic state and allow a normal pattern of growth has to be permanently maintained.

Other drugs, such as cytostatics, can affect growth. Cranial irradiation used in the treatment of tumors of the central nervous system and leukemia can damage the hypothalamic functions. Such damage has implications for the release of both hypothalamic and pituitary hormones, not the least of which is growth hormone.

Endocrine Conditions

These problems are discussed in Chapter 10.

CONCLUSION

Physical growth is the very substance of pediatric practice, modern pediatric knowledge reverberates along its axes. It provides a longitudinal, sequential, and prospective view of the human being during the most evolving and dynamic period in human life.

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REFERENCES

1. Johnston F. Somatic growth of the infant and pre-school child. In: Falkner F, Tanner JM (eds). Human Growth: A Comprehensive Treatise, 2nd ed. New York: Plenum, 1986:Vol. 2:3–24.
2. Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. Acta Paed Scand. 1989;350:70–94.
3. Brook CGD. Clinical Paediatric Endocrinology. London: Blackwell Scientific Publications, 1981.
4. Tanner JM. Revised standards for triceps and subscapular skinfolds in British children. Arch Dis Childh. 1975;50:142–145.

5. Tanner JM. Hormonal, genetic and environmental factors controlling growth. In: Harrison GA, Weiner JS, Tanner JM, Barnicot NA (eds). Human Biology: An Introduction to Human Evolution, Variation and Growth. Oxford: Oxford University Press, 1964:340–357.
6. Walton A, Hammond J. Maternal effects on growth and conformation in Shire horse–Shetland pony crosses. Proceedings of the Royal Society 1938;15B:311. In: Ounsted M, Ounsted C (eds). On Foetal Growth Rate (Its Variations and Consequences). Clinics in Developmental Medicine, no. 46. London: Spastics International Medical Publications, Heinemann, 1973:32–38.
7. Smith DW, Truog W, Rogers JE, Greitzer LJ, Skinner AL, McCann JJ, Sedwick Hervey MA. Shifting linear growth during infancy: Illustration of genetic factors in growth from fetal life through infancy. J Ped. 1976;89:223–230.
8. Prader A, Tanner JM, von Harnack GA. Catch-up growth following illness or starvation. J Ped. 1963;62:646–659.
9. Tanner JM. Growth as a target-seeking function. Catch-up and catch-down growth in man. In: Falkner F, Tanner JM (eds). Human Growth: A Comprehensive Treatise. New York: Plenum, 1986:Vol. 1:167–179.
10. Gasser T, Mueller HG, Kohler W, Prader A, Largo R, Molinari L. An analysis of the mid growth and adolescent spurts of height based on acceleration. Ann Hum Biol. 1985;12:29–148.
11. Molinari L, Largo RH, Prader A. Analysis of the growth spurt at age 7 (mid-growth spurt). Helv Paed. 1980;35:325–334.
12. Tanner JM, Cameron N. Investigation of the mid-growth spurt in height, weight and limb circumferences in single-year velocity data from the London 1966–1967 growth survey. Ann Hum Biol. 1980;7:565–577.
13. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Arch Dis Child. 1990;73:25–29.
14. Lazarus R, Baur L, Webb K, Blyth F. Adiposity and body mass indices in children: Benn's index and other weight for height indices as measures of relative adiposity. Int J Obes. 1996;20:406–412.
15. Cachera R, Sempé MF, Guilloud-Batttaille M, Patois E, Péquignot-Guggenbuhl F, Fautrad V. Adiposity indices in children. Am J Clin Nutr. 1982;36:178–184.
16. Lejarraga H, Orfila G. Estandares de peso y estatura para niñas y niños argentinos desde el nacimiento hasta la madurez. Arch Argent Ped. 1987;85:209–222.
17. Tanner JM. Use and abuse of growth standards. In: Falkner F, Tanner JM (eds). Human Growth: A Comprehensive Treatise. New York: Plenum, 1986:Vol. 1:95–112.
18. Roche SG, Fomon S. Reference data on gains in weight and length during the first two years of life. J Ped. 1991;119:355–362.
19. Martorell R, Rivera J, Kaplowitz H, Pollit E. Long term consequences of growth retardation during early childhood. In: Hernandez M, Argente J (eds). Human Growth: Basic and Clinical Aspects. International Congress Series 973. London: Excerpta Medica, 1992:143–150.
20. Barker JP. In utero programming of chronic disease. Clin Sci. 1998;95:115–128.
21. Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J (eds). The Childhood Environment and Adult Disease. New York: Wiley, 1991:38–50.
22. Fall C, Hindmarsch P, Dennison E, Kellingray S, Barker D, Cooper C. Programming of growth hormone secretion and bone mineral density in elderly men: A hypothesis. J Clin Endoc Metab. 1998;83:135–139.
23. McCance RA. Food, growth and time. Lancet. 1962;2:621.
24. Jones KL. Smith's Recognizable Patterns of Human Malformation, 4th ed. New York: Saunders, 1988.
25. Winter RM, Baraitser M. London Dysmorphology Database. Oxford: Oxford Electronic Publishers, Oxford University Press, 1990.
26. Cameron N. The prediction of adult height. In: Hauspie R, Lindgren G, Falkner F (eds). Essays on Auxology. Welwyn Garden City, UK: Castlemead Publications, 1995:126–140.
27. Lejarraga H. Validity of reported parental height in growth clinics in Buenos Aires. Ann Hum Biol. 1995;22:163–166.

28. Brandt I. Growth dynamics of low birth weight infants. Acta Paed Scand. 1985;Suppl 319:38–47.
29. Lejarraga H, Peckham C. Birth weight and subsequent growth of children exposed to congenital rubella in utero. Arch Dis Childh. 1974;49:50–58.
30. Brandt I. Growth dynamics of low birth weight infants with emphasis on the perinatal period. Acta Paed Scand. 1985;Suppl. 319:38–47.
31. Lejarraga H, Fustiñana C. Estandares de peso, longitud corporal y perímetro cefálico desde las 26 hasta las 92 semanas de edad postmenstrual. Arch Argent Ped. 1986;84:210–214.
32. Pedraza A, Cicottino N, Stutman O, Lejarraga H, Prudent L. Evaluación de un plan de seguimiento de recien nacidos de bajo peso. Estudio longitudinal durante el primer año de vida. Arch Argent Ped. 1980;78:38–40.
33. Cameron N. Human growth, nutrition and health status in sub-Saharan Africa. Year Phys Anthropol. 1991;334:211–250.
34. Waterlow JC, Buzina R, Keller W, Lane JM, Nichaman MZ, Tanner JM. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. Bull WHO. 1977;55:489–498.
35. Rolland-Cachera MF, Deheeger M, Akrout M, Bellisle F. Influence of macronutrients on adiposity development: A follow up study on nutrition and growth from 10 months to 8 years of age. Int J Obes. 1995;19:1–6.
36. Preece M. Growth in chronic diseases. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopaedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998.

3

ADOLESCENCE: SOMATIC GROWTH AND SEX DIFFERENCES

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ADOLESCENT GROWTH CYCLE

Growth at adolescence is characterized by the presence of an adolescent, or pubertal, growth spurt. Figure 3-1 shows a typical example of the growth in height of a girl between 3 and 18 years old (data from the Belgian Growth Study of the Normal Child[1-3]).

The upper part is a plot of the height-for-age data (distance curve), while the lower part shows the increments in height over 1-year intervals; that is, a proxy for velocity in growth. Actually, the yearly increments reflect average velocity in the considered interval while, strictly speaking, the term *velocity* refers to instantaneous velocity; that is, the first derivative of a smooth distance curve. Despite this, the terms *increments* and *velocities* are often intermixed, such as in this text. The horizontal bars in the graph indicate the length of the intervals over which the increments were calculated. It is common practice to calculate increments from measurements no less than 0.85 years and no more than 1.15 years apart and convert them to *whole-year* increments by taking the ratio of the difference between the two measurements and the length of the interval. Increments calculated over shorter periods reflect seasonal variation and are relatively more affected by measurement error.[4]

The growth pattern in height is characterized by a gradually decreasing (sometimes more or less constant) velocity during childhood, which is, in many children,

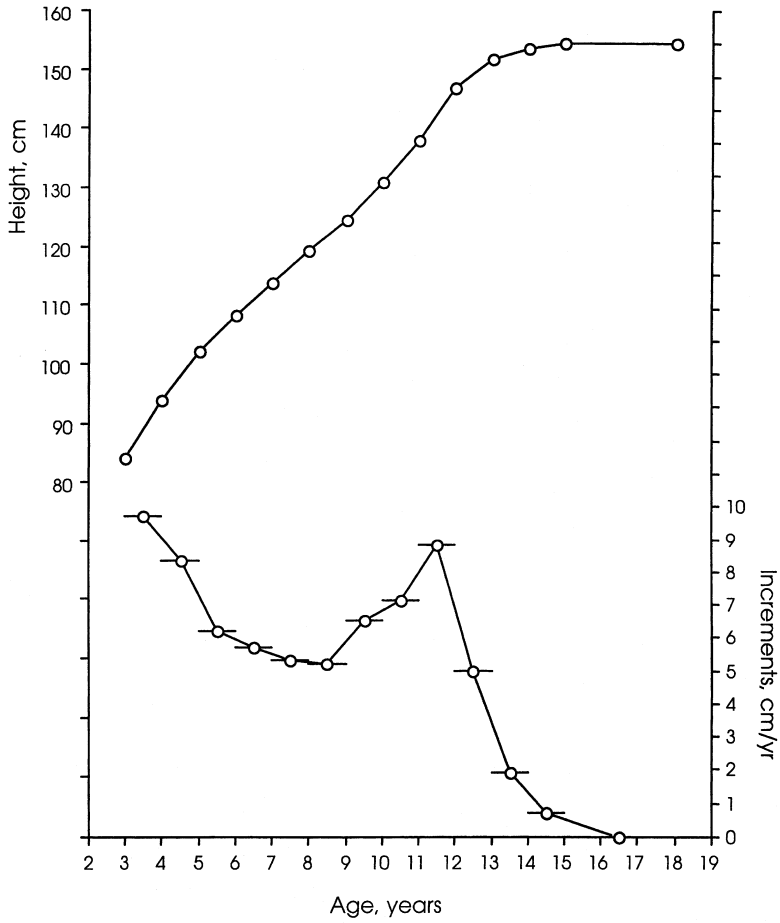


FIGURE 3-1 Growth in height of a girl (no. 29) between 3 and 18 years old. The upper part shows a plot of the height-for-age data (distance curve), while the lower part shows the yearly increments in height (velocity curve). The horizontal bars indicate the length of the intervals. (From the Belgian Growth Study of the Normal Child.)

interrupted by one or more small prepubertal (or mid-childhood) spurts[5,6] (see Chapter 2). The age at minimal velocity before puberty (age at takeoff, TO) is considered as the onset of the pubertal growth spurt. The age at takeoff varies considerably, among populations, individuals (standard deviation = about 1 year), and sexes, boys being in average 2 years later than girls in starting off their adolescent spurt. Maximum velocity in height (or peak height velocity) is reached within 3–3.5 years after the onset of the spurt. The difference in age at takeoff and age at peak velocity (PV) can be used as a measure of the duration of the adolescent spurt. After having reached a peak, the growth velocity rapidly decreases, inducing the end of the growth cycle at full maturity, around 16–17 years for girls and 18–19 years for boys in Western populations. There is a wide variation among populations, individuals and the two sexes as to the attained size at each age, the timing of events such as adolescent growth spurt, and the age at which mature size is reached. The growth curve of height (shown in Figure 3-2) is typical for all post-cranial skeletal dimensions of the body.

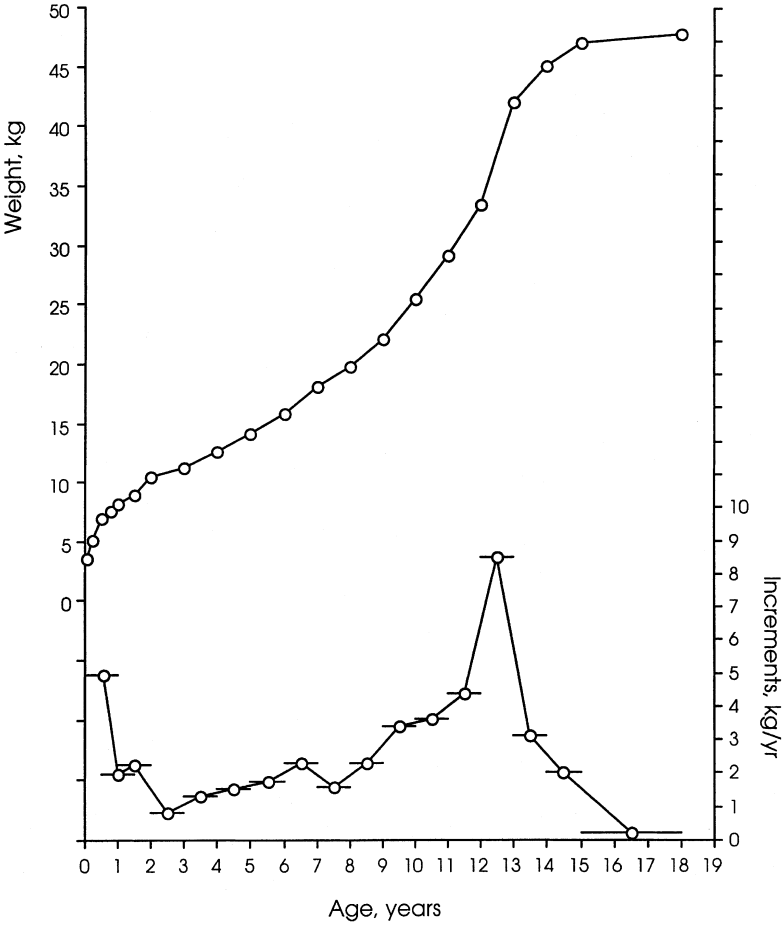


FIGURE 3-2 Increase in weight of a girl (no. 29) between 3 and 18 years old. The upper part shows a plot of the weight-for-age data (distance curve), while the lower part shows the yearly increments in weight (velocity curve). The horizontal bars indicate the length of the intervals. (From the Belgian Growth Study of the Normal Child.)

Increase in weight has a different pattern, in the sense that the start of the adolescent growth spurt in weight does not correspond with the age of minimal increment in weight before puberty. Most children show the lowest annual increase in weight in late infancy or early childhood, around 2–3 years old.[7] Thereafter, increase in weight slowly but steadily accelerates until the onset of puberty, when there is a sudden rapid increase in weight velocity. The pattern of increase in weight and weight velocity shown by the data of the girl in Figure 3-2 illustrates these typical features very well. In this example, the sudden change in velocity of weight between childhood and puberty can be identified at 11.5 years old. The precise location of the onset of the adolescent growth spurt is generally more problematic and subjective for weight than it is for height.

A third major type of growth pattern is seen in the dimensions of the head. The growth pattern for head circumference, between 1 month and 18 years of age, is exemplified in Figure 3-3. The growth of the head is very rapid during the first postnatal year, but velocity steeply falls down to levels below 1 cm/yr by the age of 2 years. Thereafter, yearly increments in head circumference fluctuate between a few millimeters and 1 cm per year and no spurt is noticeable at puberty. In the given example, 89% of the girls' adult head circumference is reached by the age of 3 years. This value is very close to the mean percentage of adult head circumference reached at 3 years of age in most populations. Very similar patterns are observed for other head dimensions such as head length and head width in both boys and girls.[8] That growth velocity of head dimensions is fairly small beyond the age of 3 years and very much corrupted by measurement error is why studies of growth and growth charts concerning the head and face are usually restricted to the period of infancy.

GROWTH MODELING AND BIOLOGICAL PARAMETERS

Most of our knowledge on the shape of the human growth curve comes from longitudinal growth data, i.e., sequential measurements of size taken at regular intervals on the same subject, such as shown in Figures 3-1 to 3-3. Serial measurements of height, for instance, form a basis for estimating the supposed underlying continuous growth curve of stature. However, recent studies have shown that frequent measurements of size (at daily or weekly intervals) with high precision techniques (such as knemometry with a measurement error of about 0.1 mm) recently showed that the underlying growth process is, at the micro-level, not as smooth as we usually assumed[9,10] (see Chapter 12). Nevertheless, for the description of the general shape of the growth curve in height, based on body measurements taken with classical techniques at intervals varying between several months and 1 year, we can readily assume that the growth process is continuous.

Various mathematical models have been proposed to estimate a smooth growth curve on the basis of a set of discrete measurements of growth of the same subject over time.[11-13] An interesting review of various approaches in modeling human growth has been given by Bogin.[14] More than 200 models have been proposed

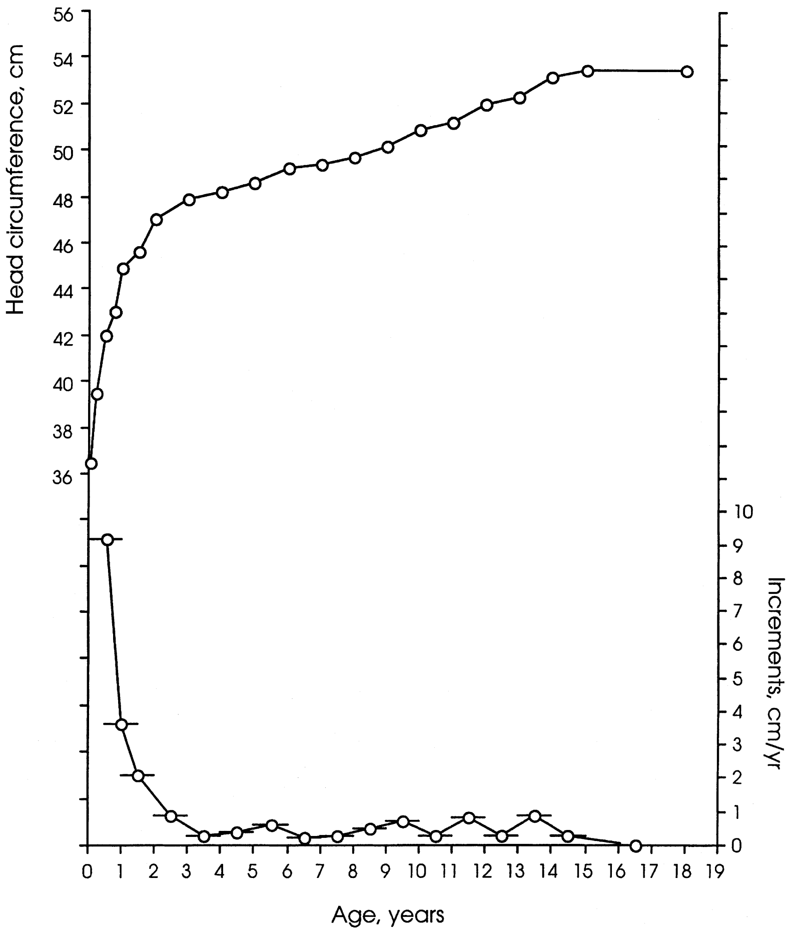


FIGURE 3-3 Growth in head circumference of a girl (no. 29) between 3 and 18 years old. The upper part shows a plot of the head circumference-for-age data (distance curve), while the lower part shows the yearly increments in head circumference (velocity curve). The horizontal bars indicate the length of the intervals. (From the Belgian Growth Study of the Normal Child.)

to describe part or all of the human growth process, only a small number of which are of practical use. The possibilities and limitations to commonly used mathematical functions for analyzing human growth have recently been discussed.[15,16] Here, we concentrate on the Preece-Baines model 1 (PB1), which has been proven to be a very robust model in describing the adolescent growth cycle on the basis of growth data covering the period from 2–5 years of age up to full maturity.[17] Whenever longitudinal data from birth to adulthood is at hand, one can better estimate the whole growth curve by means of the triple logistic function[18] or the JPA-2 function,[19] for instance.

The mathematical expression of Preece-Baines model 1 is

$$y = h_1 - \frac{2(h_1 - h_\theta)}{e^{s_0(t-\theta)} + e^{s_1(t-\theta)}}$$

with y = height in centimeters; t = age in years; and h_1, h_θ, s_0, s_1, and θ are the five function parameters. Parameters of nonlinear growth models usually allow some functional interpretation of the growth curve. In the case of PB1, parameter h_1 is the upper asymptote of the function and thus corresponds to an estimate of mature size. Parameter θ is very highly correlated with age at peak velocity. Parameter h_θ is the size at age θ. Parameters s_0 and s_1 are rate constants controlling, respectively, prepubertal and pubertal growth velocity.

The parameter estimation of nonlinear growth functions like the PB1 curve are usually obtained by nonlinear least-squares techniques based on numerical minimization algorithms, such as the simplex,[20] Marquardt,[21] and Gauss[22] methods. Most statistical and several graphical software programs now offer the possibility of nonlinear regression analysis of user-entered functions.

The outcome of modeling an individual's serial growth data is a set of values for the function parameters (five in the case of PB1). Hence, growth modeling (or curve fitting) is a technique by which longitudinal growth data can be summarized in a limited number of constants, which have the same meaning for all subjects, thus allowing easy comparison among individuals. By entering the values of the function parameters into the model, one can graph the individual's smooth growth curve. Likewise, when entering the parameter values into the first derivative of the growth model, one obtains an estimation of the instantaneous growth velocity. The growth velocity function for PB1 follows:

$$y' = \frac{2(h_1 - h_\theta)(s_0 e^{s_0(t-\theta)} + s_1 e^{s_1(t-\theta)})}{(e^{s_0(t-\theta)} + e^{s_1(t-\theta)})^2}$$

Figure 3-4 shows a plot of the PB1 function fitted to the distance data for height of the same girl as in previous figures. The lower part of Figure 3-4 shows a plot of the yearly increments together with the instantaneous velocity curve obtained as the mathematical first derivative of the fitted distance curve. The values of the function parameters for this example are given in Table 3-1.

The standard error of estimate (= square root of the residual variance) is often used as a measure of the goodness of the fit:

$$\text{Standard error of estimate} = \sqrt{\frac{\sum_{i=1}^{N}(y_i - \hat{y}_i)^2}{N-k}}$$

with y_i, the height at x_i; $\hat{y}_i$, the value of the fitted curve at x_i; N, the number of height measurements; and k, the number of parameters in the model (five in the case of PB1). It is generally accepted that a fitted curve adequately describes the growth

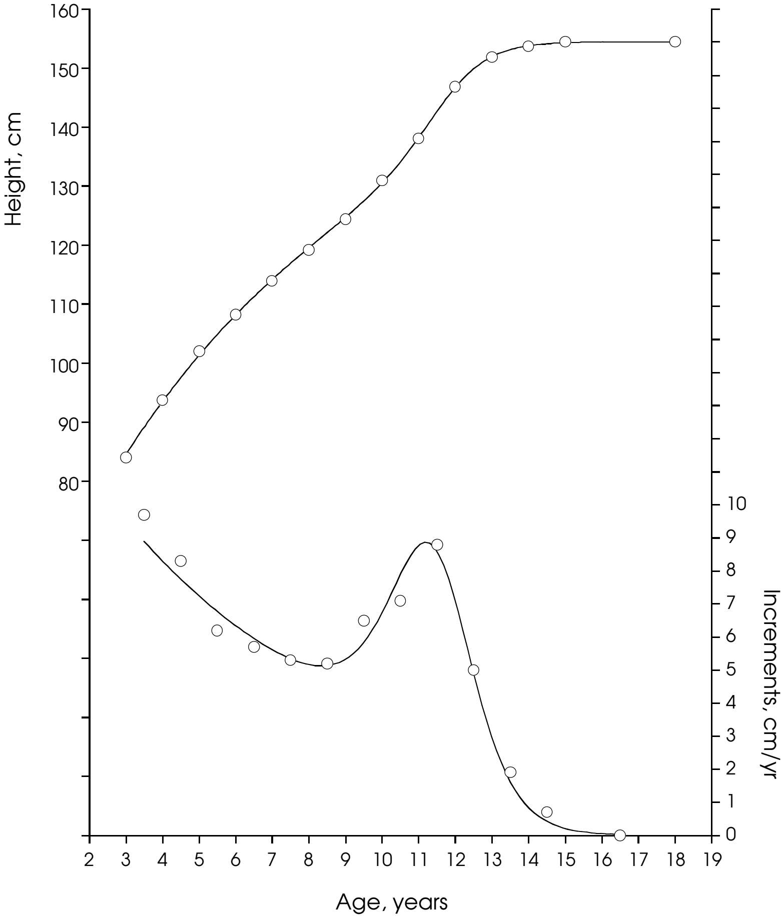


FIGURE 3-4 Growth in height of a girl (no. 29) between 3 and 18 years old. The upper part shows a plot of the height-for-age data together with the Preece-Baines model 1, while the lower part shows the yearly increments in weight with the first derivative of the fitted curve. (From the Belgian Growth Study of the Normal Child.)

data if the standard error of estimate is of the same order of magnitude as the measurement error of the trait under consideration (typically 0.5 cm for stature during childhood and adolescence). Systematic bias can be estimated as the test runs.[23] Large values of the standard error of estimate and systematic bias may, among others, occur with

- Low-precision data (large measurement error, inexperienced measurers, large intermeasurer variation, inadequate measuring devices, and so on).

TABLE 3-1 Function Parameters and Biological Parameters Obtained by Fitting Preece-Baines Model 1 to the Height Data of Girl No. 29 (taken from the Belgian Growth Study of the Normal Child[1])

h_1	154.4 cm^2
h_θ	143.7 cm^2
s_0	0.1374
s_1	1.450
θ	11.63 yr
Residual variance	0.144 cm^2
Standard error of estimate	0.380 cm^2
Age at takeoff	8.33 yr
Height at takeoff	121.2 cm^2
Velocity at takeoff	5.1 cm^2/yr
Age at peak velocity	11.18 yr
Height at peak velocity	139.8 cm^2
Velocity at peak velocity	8.9 cm^2/yr
Adolescent gain	33.2 cm^2

- Inappropriate age ranges of the growth data for the chosen model (each model is designed to fit growth data in a particular age range, including data beyond that age range results in bad curve fittings).
- Inappropriate models for the type of variable (models designed for postcranial skeletal dimensions, such as the PB1 function, for instance, are inappropriate for fitting head dimensions or weight).
- The presence of particular features in the growth data that cannot be described by the growth model (prepubertal growth spurt(s), unusual variations of growth rate in pathological growth).

Growth variables that do not necessarily have a monotonously increasing pattern (such as weight, body mass index, skinfolds) cannot be successfully described by structural models such as nonlinear growth functions. Nonstructural approaches, such as polynomials, smoothing splines, and kernel estimations are more appropriate for these kinds of traits.[24,25]

In addition to producing a smooth continuous curve for growth and growth velocity and summarizing the growth data into a limited number of constants, the main goals of mathematical modeling of human growth data are to estimate

- Growth between measurement occasions (interpolation).
- Milestones of the growth process (the so-called biological parameters), such as age, size, and velocity at takeoff and peak velocity, for instance.
- The "typical average" curve in the population by means of the mean-constant curve (see later).

Table 3-1 also shows a number of biological parameters that were derived from the fitted curve shown in Figure 3-4. Note that adult height estimated by the PB1 fit is equal to h_1 = 154.4 cm. Biological parameters, obtained by fitting a growth model, characterize the shape of the human growth curve and form a basis for studies of genetic and environmental factors that control the dynamics of human growth.

One should be suspicious about estimations of final size by structural growth models in cases where the growth data give no clear indication that the end of the growth phase is nearby. Estimated final height, for instance, is likely to be fairly unreliable if the last yearly increment in the growth data exceeds 2 cm/yr. Least-squares techniques are hopelessly weak in fitting parameters beyond the observation range and thus inapt to extrapolate. Analogous problems may arise when the lower bound of the age range does not include the takeoff of the adolescent growth spurt. In such a situation, the estimation of the age at takeoff and all derived biological parameters by a PB1 fit are not under control of the data and likely to be erroneous. A possible solution to the problem of extrapolation, like the prediction of mature stature (and also to the problem of incomplete data), is by using Bayesian estimations instead of least-squares techniques for the parameter estimation.[18,26]

TEMPO OF GROWTH

The famous American anthropologist Franz Boas, in the beginning of the twentieth century, already described that "some children are throughout their childhood further along the road to maturity than others."[27,28] Indeed, individuals not only vary considerably in size but also in tempo of growth; that is, the speed at which they reach mature size. Tempo of growth, or maturation rate, is correlated with other markers of maturation, such as secondary sexual characteristics and bone age.

Figure 3-5 shows a theoretical example of the main effects of variation in tempo on the shape of the human growth curve. The figure shows the distance and velocity curves for the stature of typical early, average, and late-maturing children having the same size at birth and adulthood. These three theoretical subjects have, so to speak, the same potential for reaching a certain mature size, but they differ considerably in height at all ages along their growth period and in the shape of their growth pattern. We can see that the early maturer reaches final size earlier and is taller than the average maturer throughout childhood and adolescence. In turn, the average maturer reaches adult size earlier and is taller than the late maturer. The effects of differences in tempo of growth on attained height increase with age and are most apparent in periods where the slope of the growth curve is steepest. Therefore, variation in maturation rate affects attained height mostly during the adolescent period.

The relationship between the shape of the growth curve and the tempo of growth, as depicted in the preceding theoretical example, is also reflected in real population data. Longitudinal studies have repeatedly shown that little or no correlation exists between the timing of the pubertal spurt and adult stature; that is, early, average, and late-maturing children reach, on average, the same adult height.[25,29-33] This

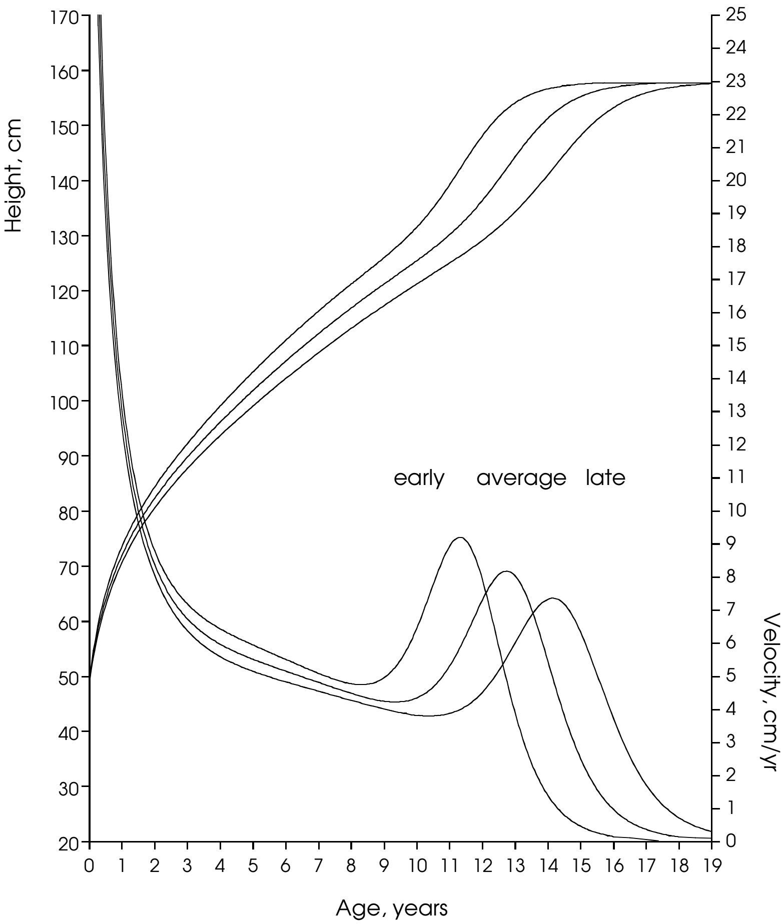


FIGURE 3-5 Effect of tempo on the pattern of growth: A theoretical example.

is also true for other postcranial body dimensions[29] but not for weight. Early maturing children are, on average, heavier than late-maturing children.[27] The shorter growth cycle in early maturers is compensated by a slightly but consistently greater growth velocity during childhood and, particularly, by a more intense pubertal growth spurt. The opposite is seen in late-maturing children. This relationship is reflected in the negative correlation between peak velocity and age at peak velocity in height and several other traits.[25,34,35]

Studies on longitudinal growth of twin and family data have shown that tempo of growth is to a great extent genetically determined.[13,36-39] In a more recent longitudinal growth study of monozygotic and dizygotic male twins, Hauspie et al.[40] found a strong genetic component in the variance of various biological parameters characterizing the shape of the human growth curve; in particular, for age at peak velocity, reflecting tempo of growth. Similar findings were reported by Byard, Guo, and Roche[41] on the basis of an analysis of familial resemblance in growth curve parameters in the Fels Longitudinal Growth Study. Tanner[42] suggested that both the growth status and the tempo of growth are under genetic control but that the genetic factors might be quite different. Despite the strong genetic control over tempo of growth, there is also evidence that the human body can adapt to adverse environmental conditions by slowing down the developmental growth rate, probably allowing a child to better cope with the physiological and metabolic requirements for a balanced development in suboptimal situations. If the adverse conditions are reversed, then a child usually restores its growth deficit by a period of rapid growth to regain its original "growth channel," the so-called catch-up growth.[43-45] If, however, the environmental stresses hold on for a long period or throughout the whole growth cycle, the resulting effect on growth may be a pattern that is typical for late-maturing children. Typical examples of this were found for children exposed to chronic mild undernutrition,[46] chronic diseases such as asthma,[47] psychosocial stress,[48-50] socioeconomic deprivation,[51] and living at high altitude.[52] Those children tend to be slightly delayed in reaching the adolescent growth spurt, in achieving sexual maturity, and in attaining their final size. Final stature is usually not affected (i.e., is compatible with the population average) unless the long-lasting adverse conditions are too severe.[45]

INDIVIDUAL VERSUS AVERAGE GROWTH

Much of our knowledge on children's growth comes from longitudinal studies, that is, data comprising series of growth measurements of the same subjects over time, allowing to establish part or the whole of the individual growth pattern. However, the great majority of growth studies are cross-sectional; that is, based on single growth measurements taken from individuals who differ in age. Cross-sectional growth data allow to estimate the central tendency and variation of growth variables at each age in the population and to construct smooth centile lines showing the "average" growth and the limits of "normal" variation in that population. These centile lines form the basis of growth standards and reference curves (see Chapter 18). Despite the immense merits of cross-sectional growth surveys in constructing growth standards and in epidemiological studies of the genetic and environmental factors involved in growth, they can give only a static picture of the population variation in growth variables and are hopelessly weak in providing information on the dynamics of individual growth patterns over time.

The variation in the tempo of growth means that a cross-sectional mean curve, to some extent, smoothes out the phenomenon of the adolescent growth spurt. Figure 3-6 illustrates this effect very clearly on the basis of the longitudinal growth curves of two boys (taken from Chrzastek-Spruch's unpublished data on the Lublin Longitudinal Growth Study[53]), compared to the cross-sectional mean of their growth

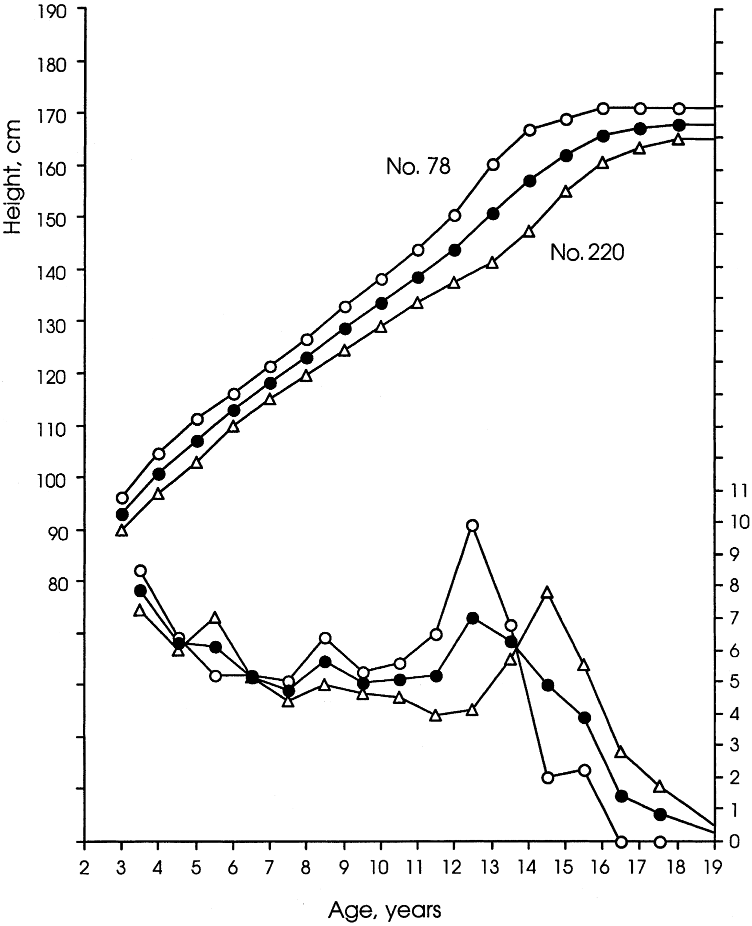
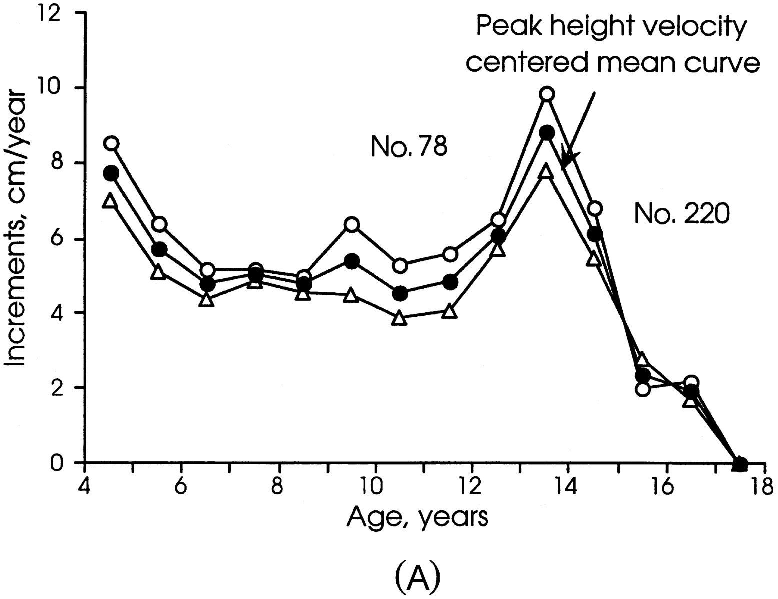


FIGURE 3-6 Cross-sectional means of distance and velocity curves. An example of two boys. (Data from Chrzastek-Spruch's unpublished report on the Lubin Longitudinal Growth Study.[53])

data. The two subjects differ in timing of their adolescent growth spurt, the age at maximum increment in height being at, respectively, 12.5 and 14.5 years of age. By taking the averages of the heights at each age, without taking account of this difference in timing of the adolescent growth spurt, one comes up with an average curve that does not show the steep slope at adolescence, seen in each individual curve. The effect of taking the cross-sectional mean becomes even more striking by a comparison of the yearly increments in height of the two curves with the average of these yearly increments. While the two individuals show a clear adolescent spurt with a maximum yearly increment in height of respectively 9.9 and 7.8 cm/yr, the cross-sectional mean of these curves is much flatter. The peak of the mean velocity curve is lower than in the individual curves and the "spurt" is spread out over a longer period than in the two individuals, a phenomenon denoted as the "phase-difference" effect.[7]

Although the example shown in Figure 3-6 is based on averages of longitudinal growth data, it is exactly what happens with the pattern of the means in cross-sectional growth data and the pattern of the increments of the means. By the way, the mean velocity curve in Figure 3-6 corresponds exactly to a plot of the increments of the means. This illustrates that the pattern of individual growth differs a lot from the pattern of cross-sectional mean growth, especially during adolescence. It is also the reason why the growth records of an individual over time do not match any of the centile lines shown by cross-sectional growth charts and why such charts are not useful to evaluate the normality of the *pattern* of growth over time. Pure cross-sectional growth standards are also called *unconditioned for tempo*. The differences between individual and average growth have long been recognized (Boas, 1892, and Shuttleworth, 1937, are cited by Tanner[28]), but it was not until the mid-1960s that Tanner, Whitehouse, and Takaishi[7,54] introduced *tempo-conditioned* growth standards for height, weight, height velocity, and weight velocity based on longitudinal data of the British population. In addition to the classical centile distribution for attained size and velocity at each age, these references also show the "normal" variation in the *shape* of the growth curves. Their technique to produce the latter reference curves (the so-called tempo-conditioned standards) was based essentially on an analysis of the longitudinal growth data after centering each individual's growth data around the age at peak velocity.

Figure 3-7A illustrates this technique and its effect on average height velocity of the two boys shown in Figure 3-6, after their height measurements were peak height velocity centered. The so-obtained mean velocity curve indeed has a pattern that can be considered representative for both individuals; that is, with an age at peak velocity and a peak velocity that is the average of the two subjects. Later on, Tanner and Davies[4] produced clinical longitudinal standards for height and height velocity in North American children using the same graphical principle as in their 1966 British standards. Wachholder and Hauspie,[2,3] on the contrary, used a technique, derived from curve fitting, to achieve similar goals when producing clinical standards for growth and growth velocity in the Belgian population. They used "mean-constant" curves to estimate the typical average pattern of growth in the population. The mean-constant curves were obtained by fitting the Preece-Baines model 1 to each individual in the sample and feeding the mean values of the function parameters into the model. The resulting mean-constant curve represents the growth pattern of the typical average child in the population; that is, with a peak velocity and an age at peak velocity characteristic or typical for the group.[12] Hence, a mean-constant curve is very much like the average of peak velocity centered curves. Figure 3-7B shows the PB1 velocity curves of the same two boys together with their mean-constant curve. Note that the PB1 curves slightly underestimate peak velocity, a minor weakness of the PB1 model that has been acknowledged elsewhere.[16]



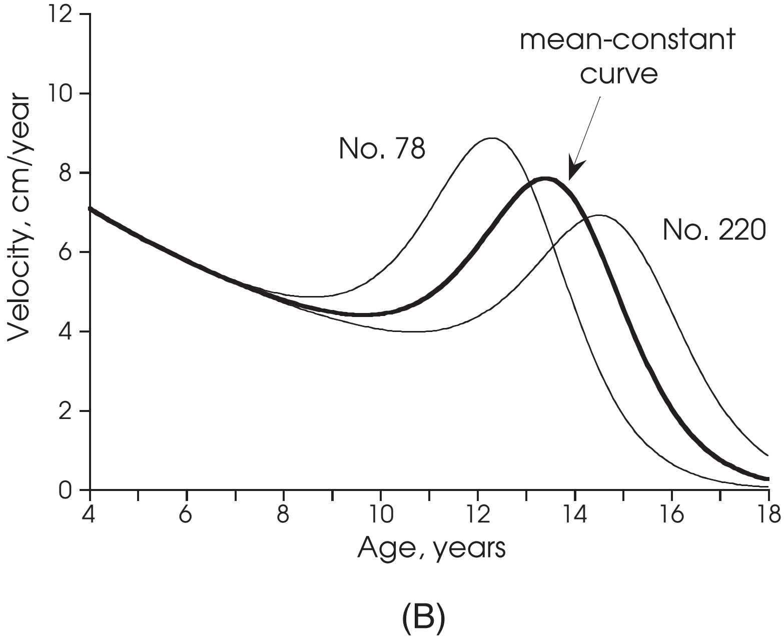


FIGURE 3-7 (A) Peak height velocity-centered plots of the yearly increments of two boys together with the cross-sectional mean of the two curves. (B) PB1 velocity curves of two boys together with the mean-constant curve. (Data from Chrzastek-Spruch's unpublished report on the Lubin Longitudinal Growth Study.[53])

SEX DIFFERENCES IN GROWTH

It is well known that women are on the average smaller than men for all linear body dimensions, in particular height, sitting height, and leg length.[27] Although some differences between boys and girls may already be present at birth, they remain, in general, small until the time that girls start their pubertal growth spurt. Because of the 2-year difference in age of onset of the pubertal spurt, 11-, 12-, and 13-year-old European girls are, on average, taller and heavier than the boys of the same age.[55] Some findings suggest a positive correlation between the amount of sex differences in adult size and the sex average for size.[56,57] However, Eveleth[58] found a relatively larger sex difference in adult stature in Amerindians, who have a relatively smaller adult size. Similar findings were reported for Asian Indians.[59] Eveleth postulated that genetic factors probably play an important role in establishing mature size and sex differences, although it is conceivable that boys are treated better in these societies than girls, allowing them to better express their genetic potential than girls.

Most of our knowledge on sex differences in growth is derived from cross-sectional data, which allow us to estimate fairly accurately the sex differences during infancy, childhood, and adulthood, as well as the points of intersection between the male and female average growth curve. However, for reasons explained already, cross-sectional data poorly reflect individual growth and longitudinal data is needed to understand the manner in which sex differences in size arise during the growth process.[34] Using mean-constant curves, allowing estimation of the typical male and female curves in the population, one can analyze the dynamics of the sex dimorphism in human growth. As an example, Figure 3-8 shows the sex differences in the mean-constant curves for Belgian boys and girls. Note that takeoff is pointed out by a black dot. We consider prepubertal growth as the size achieved up to the age at takeoff, while adolescent growth (or adolescent gain) is the amount of growth achieved between takeoff and adulthood. Figure 3-8 illustrates how the sex difference in adult size (D) can be decomposed into three additive components:

DA: The difference in adolescent gain between boys and girls.

DP: The difference in prepubertal growth; that is, the difference in size at the girls' takeoff.

DT: The amount of growth achieved by the boys between the girls' and the boys' takeoffs.

Using this technique, Hauspie et al.[59] analyzed the dynamics of the sex differences in height, sitting height, shoulder width, and hip width in British children. The results are summarized in Table 3-2.

It can be seen that the largest contribution to sex differences in adult height comes from the later onset of the pubertal growth spurt in boys than in girls (DT = 7.9 cm). Sex differences in prepubertal growth (DP = 2.0 cm) and in adolescent gain (DA = 2.0 cm) are relatively smaller. Slightly different values for these components may be found in other populations. In West Bengal children, for instance, Hauspie

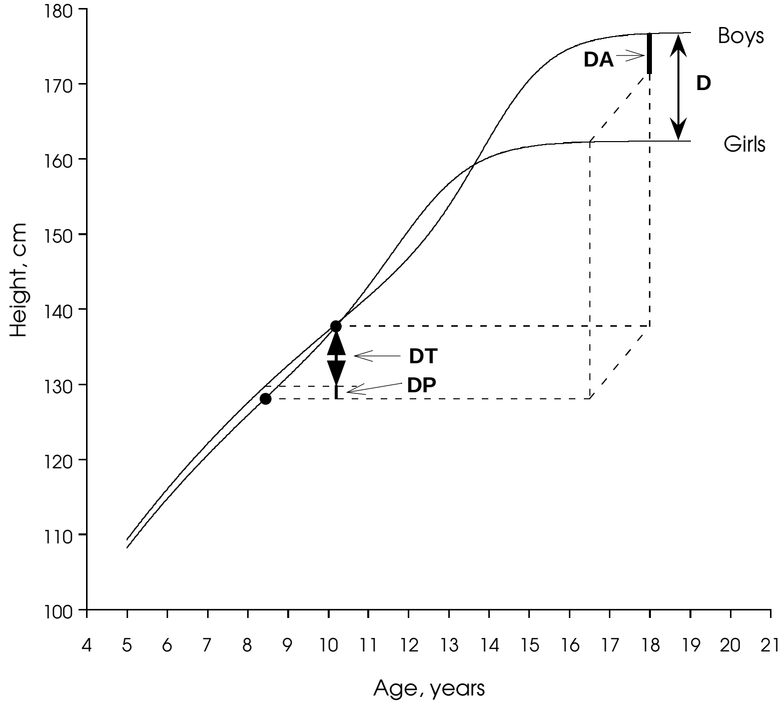


FIGURE 3-8 Decomposition of sex differences in adult stature into three additive components (see text for explanation of abbreviations).

et al.[59] found a larger sex difference in adult height (D = 14.2 cm), mainly due to a relatively more important adolescent gain than in the British children, whereas data for the Belgian population show, such as for the British children, a relatively larger contribution of DT to the sex differences in adult height.[60] Table 3-2 shows that the decomposition of adult sex differences in sitting height is percentagewise

TABLE 3-2 Decomposition of Sexual Dimorphism in Adult Size of Height, Sitting Height, Shoulder Width, and Hip Width into Three Additive Components (see text for explanation of abbreviations): A British Sample

	Height (cm)	Sitting Height (cm)	Shoulder Width (cm)	Hip Width (cm)
D	12.0	4.5	3.7	–0.6
DA	2.0	0.7	1.7	–2.0
DP	2.1	0.3	0.3	–0.1
DT	7.9	3.5	1.7	1.5

similar to that seen for stature. On the contrary, for shoulder width boys have a relatively larger increase during adolescence than girls. As far as hip width is concerned, adult sex differences are almost negligible. Prepubertal differences in hip width are also nonexistent, and the greater adolescent gain in hip width of the girls (DA = –1.0 cm) is counterbalanced by the amount of growth in hip width of boys due to their prolonged prepubertal growth period. In conclusion, it can be said that the adult sex differences in longitudinal body dimensions are attributable mainly to the boys' longer prepubertal growth cycle. Sex differences in shoulder width is in equal amounts due to the delay in onset of the growth spurt and greater adolescent gain in the boys. Finally, sex differences in hip width are negligible in adulthood and also before puberty. The slightly greater increase in hip width during adolescence by the girls is largely compensated for by the boys' gain in hip width during their longer prepubertal period.

REFERENCES

1. Graffar M, Asiel M, Emery-Hauzeur C. La croissance de l'enfant normal jusqu'à trois ans: analyse statistique des données relatives au poids et à la taille. Acta Paed Belg. 1962;16:5–23.
2. Wachholder A, Hauspie RC. Clinical standards for growth in height of Belgian boys and girls aged 2 to 18 years. Int J Anthropol. 1986;1:339–348.
3. Hauspie RC, Wachholder A. Clinical standards for growth velocity in height of Belgian boys and girls, aged 2 to 18 years. Int J Anthropol. 1986;1:327–338.
4. Tanner JM, Davies PW 1985. Clinical longitudinal standards for height and height velocity for North American children. J Ped. 107:317–329.
5. Butler GE, McKie M, Ratcliffe SG. An analysis of the phases of mid-childhood growth by synchronisation of growth spurts. In: Tanner JM (ed). Auxology 88, Perspectives in the Science of Growth and Development. London: Smith-Gordon, 1989:77–84.
6. Hauspie RC, Chrzastek-Spruch H. The analysis of individual and average growth curves: Some methodological aspects. In: Duquet W, Day JAP (eds). Kinanthropometry IV. London: E & FN Spon, 1993:68–83.
7. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Part I. Arch Dis Child. 1966;41:454–471.
8. Twiesselmann F. Développement biométrique de l'enfant à l'adulte. Paris: Librairie Maloine, 1969.
9. Hermanussen M. 1998. The analysis of short-term growth. Hormone Research. 49:53–64.
10. Lampl M. Saltation and Stasis in Human Growth: Evidence, Methods and Theory. London: Smith-Gordon, 1999.
11. Marubini E, Milani S. Approaches to the analysis of longitudinal data. In: Falkner F, Tanner JM (eds). Human Growth—A Comprehensive Treatise, 2nd ed. New York: Plenum, 1986:79–94.
12. Hauspie RC. Mathematical models for the study of individual growth patterns. Revue d'Epidém et Santé Pub. 1989;37:461–476.
13. Hauspie RC. Curve fitting. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998:114–115.
14. Bogin B. Patterns of Human Growth. Cambridge: Cambridge University Press, 1988.
15. Hauspie RC, Lindgren G, Tanner JM, Chrzastek-Spruch H. Modelling individual and average human growth data from childhood to adulthood. In: Magnusson D, Bergman LR, Törestad B (eds). Problems and Methods in Longitudinal Research—Stability and Change. Cambridge: Cambridge University Press, 1991:28–46.

16. Hauspie R, Chrzastek-Spruch H. Growth models: Possibilities and limitations. In: Johnston FE, Zemel B, Eveleth PB (eds). Human Growth in Context. London: Smith-Gordon, 1999:15–24.
17. Preece MA, Baines MK. A new family of mathematical models describing the human growth curve. Ann Hum Biol. 1978;5:1–24.
18. Bock RD. Predicting the mature stature of preadolescent children. In: Susanne C (ed). Genetic and Environmental Factors During the Growth Period. New York and London: Plenum, 1984: 3–19.
19. Jolicoeur P, Pontier J, Abidi H. Asymptotic models for the longitudinal growth of human stature. Am J Hum Biol. 1992;4:461–468.
20. Nelder JA, Mead R. A simplex method for function minimisation. Computer J. 1965;7:308–313.
21. Marquardt DW. An algorithm for least squares estimation of non-linear parameters. J Soc Indust Appl Math. 1963;11:431–441.
22. Bard Y. Non-linear Parameter Estimation. New York: Academic Press, 1974.
23. Siegel S. Nonparametric Statistics for the Behavioral Sciences. London: McGraw-Hill, 1956.
24. Gasser T, Köhler W, Müller HG, Kneip A, Largo R, Molinari L, et al. Velocity and acceleration of height growth using kernel estimation. Ann Hum Biol. 1984;11:397–411.
25. Largo RH, Gasser T, Prader A, Stützle W, Huber PJ. Analysis of the adolescent growth spurt using smoothing spline functions. Ann Hum Biol. 1978;5:421–434.
26. Bock RD, Thissen DM. Statistical problems of fitting individual growth curves. In: Johnston FE, Roche AF, Susanne C (eds). Human Physical Growth and Maturation. New York and London: Plenum, 1980:265–290.
27. Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications; Springfield, IL: Charles C Thomas, 1962.
28. Tanner JM. A History of the Study of Human Growth. Cambridge: Cambridge University Press, 1981.
29. Cameron N, Tanner JM, Whitehouse RH. A longitudinal analysis of the growth of limb segments in adolescence. Ann Hum Biol. 1982;9:211–220.
30. Zacharias L, Rand WM. Adolescent growth in height and its relation to menarche in contemporary American girls. Ann Hum Biol. 1983;10:209–222.
31. Marshall WA, Tanner JM. Puberty. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 2. New York: Plenum, 1986:171–209.
32. Malina RM, Bouchard C. Growth, Maturation and Physical Activity. Champaign, IL: Human Kinetics, 1991.
33. Bielicki T, Hauspie RC. On the independence of adult stature from the timing of the adolescent growth spurt. Am J Hum Biol. 1994;6:245–247.
34. Tanner JM, Whitehouse RH, Marubini E, Resele LF. The adolescent growth spurt of boys and girls of the Harpenden study. Ann Hum Biol. 1976;3:109–126.
35. Hauspie R. Adolescent growth. In: Johnston FE, Roche AF, Susanne C (eds). Human Physical Growth and Maturation: Methodologies and Factors. New York and London: Plenum, 1980:161–175.
36. Sharma JC. The genetic contribution to pubertal growth and development studies by longitudinal growth data on twins. Ann Hum Biol. 1983;10:163–171.
37. Mueller WH. The genetics of size and shape in children and adults. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 3. Methodology, Ecological, Genetic, and Nutritional Effects on Growth. New York: Plenum, 1986:145–168.
38. Hauspie RC, Das SR, Preece MA, Tanner JM. Degree of resemblance of the pattern of growth among sibs in families of West Bengal (India). Ann Hum Biol. 1982;9:171–174.
39. Hauspie RC. The genetics of child growth. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998:124–128.
40. Hauspie RC, Bergman P, Bielicki T, Susanne C. Genetic variance in the pattern of the growth curve for height: a longitudinal analysis of male twins. Ann Hum Biol. 1994;21:347–362.

41. Byard PJ, Guo S, Roche AF. Family resemblance for Preece-Baines growth curve parameters in the Fels Longitudinal Growth Study. Am J Hum Biol. 1993;5:151–157.
42. Tanner JM. Foetus into Man: Physical Growth from Conception to Maturity. London: Open Books, 1978.
43. Golden MHN. Catch-up growth in height. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998:346–347.
44. Prader A, Tanner JM, Von Harnack GA. Catch-up growth following illness or starvation. J Ped. 1963;62:646–659.
45. Tanner JM. Growth as a target-seeking function—catch-up and catch-down growth in man. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 1. Developmental Biology, Prenatal Growth. New York: Plenum, 1986:167–179.
46. Hansen JDL, Freesemann C, Moodie AD, Evans DE. What does nutritional growth retardation imply? Ped. 1971;47:299–313.
47. Hauspie R, Susanne C, Alexander F. Maturational delay and temporal growth retardation in asthmatic boys. J Aller and Clin Immun. 1977;89:200–206.
48. Skuse DH. Growth and psychosocial stress. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998:341–342.
49. Powell GF, Brasel JA, Blizzard RM. Emotional deprivation and growth retardation simulating idiopathic hypopituitarism. N Engl J Med. 1967;276:1271–1283.
50. Widdowson EM. Mental contentment and physical growth. Lancet. 1951;1:1316–1318.
51. Bielicki T. Physical growth as a measure of the economic well-being of populations: The twentieth century. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 3. Methodology, Ecological, Genetic, and Nutritional Effects on Growth. New York: Plenum, 1986:283–305.
52. Malik SL, Hauspie R. Age at menarche among high altitude Bods of Ladakh (India). Hum Biol. 1986;58:541–548.
53. Chrzastek-Spruch H, unpublished data. Growth patterns of two girls from the Lublin Longitudinal Growth Study.
54. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Part II. Arch Dis Child. 1966;41:613–635.
55. Eveleth PB, Tanner JM. Worldwide Variation in Human Growth. Cambridge: Cambridge University Press, 1990.
56. Hall RL. Sexual dimorphism for size in seven nineteenth century northwest coast populations. Hum Biol. 1978;50:159–171.
57. Valenzuela CY, Rothhammer F, Chakraborty R. Sex dimorphism in adult stature in four Chilean populations. Ann Hum Biol. 1978;5:533–538.
58. Eveleth PB. Differences between ethnic groups in sex dimorphism of adult height. Ann Hum Biol. 1975;2:35–39.
59. Hauspie R, Das SR, Preece MA, Tanner JM, Susanne C. Decomposition of sexual dimorphism in adult size of height, sitting height, shoulder width and hip width in a British and West Bengal sample. In: Ghesquire J, Martin RD, Newcombe F (eds). Human Sexual Dimorphism. London and Philadelphia: Taylor & Francis, 1985:207–215.
60. Koziel SK, Hauspie RC, Susanne C. Sex differences in height and sitting height in the Belgian population. Int J Anthropol. 1995;10:241–247.

4

PUBERTY

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INTRODUCTION

Puberty refers to the onset of adult reproductive capacity. As a milestone in human development, puberty is quite dramatic, involving a rapid transformation of anatomy, physiology, and behavior. Other than pregnancy, it is probably the most abrupt and encompassing developmental transition that human beings undergo between birth and death. It is also a transition of deep cultural significance in most societies around the world, often marked by special rituals and ceremonies.[1] As dramatic as it is, however, puberty is not an instantaneous threshold or a discrete state but a process integrated more or less smoothly with the antecedent and consequent developmental phases of immaturity and adulthood. As a result it is, in fact, quite difficult to clearly identify either the beginning or the end of the pubertal period. Unlike the metamorphosis of an insect through discrete morphological stages, the human organism is transformed from its immature to its mature state through a rapid and profound, but essentially continuous, trajectory of change.

The central feature of human puberty is the maturation of the primary reproductive endocrine axis, composed of the hypothalamus, pituitary gland, and gonad. This three-part system—referred to in general as the hypothalamic-pituitary-gonadal (HPG) axis, or specifically as the hypothalamic-pituitary-ovarian (HPO) axis in females and the hypothalamic-pituitary-testicular (HPT) axis in males—controls the reproductive functions of the organism, including the production and maturation of gametes and the activity of the other components of the reproductive tract necessary for reproduction in both sexes. The secondary features of human puberty include the development of secondary sexual characteristics, the development of sexually dimorphic anatomical features, the acceleration and ultimate cessation of linear growth, quantitative changes in the function of many other endocrine systems (particularly those involved in the partitioning of metabolic effort), and changes in behavior and its substrates, including the libido. Virtually all the secondary changes of puberty are downstream consequences of the primary maturation of the HPG axis. In particular, the actions of the steroid hormones produced by the ovaries and testes are directly involved in most aspects of pubertal development. A few physiological changes associated with puberty precede HPG axis activation, although their status as releasers or causes of the primary events of puberty is uncertain.

An understanding of human puberty, therefore, begins with an understanding of the functioning of the HPG axis and its developmental trajectory.[2–5] Secondary features of puberty can then be viewed as consequences of this central developmental transformation. While this approach can successfully integrate much of what we know about human puberty—its normal course and variability, its mechanisms, and its associated pathologies—it also highlights areas of ongoing controversy, contemporary research, and lingering ignorance.

HPG AXIS

The hormonal signals that flow between the components of the HPG axis coordinate the central processes of reproductive biology and integrate them with other features of the organism's anatomy, physiology, and behavior. The central features of this regulatory system can be sketched out in rather simple terms, but the student should be aware the details are far more complex and convoluted than implied by such summaries (Figure 4-1).

The hypothalamus serves as the main enabling center for the rest of the HPG axis. Its primary signal is a small peptide hormone variously known as *gonadotropin-releasing hormone* (GnRH) and *luteinizing-hormone-releasing hormone* (LHRH).[6,7] It is secreted by the median eminence of the hypothalamus into the tiny portal vascular system that connects this region of the brain to the anterior pituitary gland.[8] The effect of GnRH is to stimulate production and release of two protein hormones from the pituitary, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[9,10] GnRH must be released in a pulsatile fashion to have its ordinary stimulatory effect on the pituitary. In adults, the hypothalamus releases GnRH pulses about once an hour, controlled by a pulse generator located in the region of the arcuate nucleus.[11] Surgical manipulation of rhesus monkeys has demonstrated that pulse frequencies much faster or slower than this result in a suppression of gonadotropin release by the pituitary.[12,13] On the other hand, a constant regime of exogenously administered hourly GnRH pulses is sufficient to sustain normal functioning of the axis both in experimental animals and humans suffering pathological disruptions of hypothalamic function. In particular, it is notable that a constant regime of circhoral GnRH pulses is sufficient to maintain full ovarian cyclicity in both rhesus monkeys and women.[14–17] These observations give rise to the concept

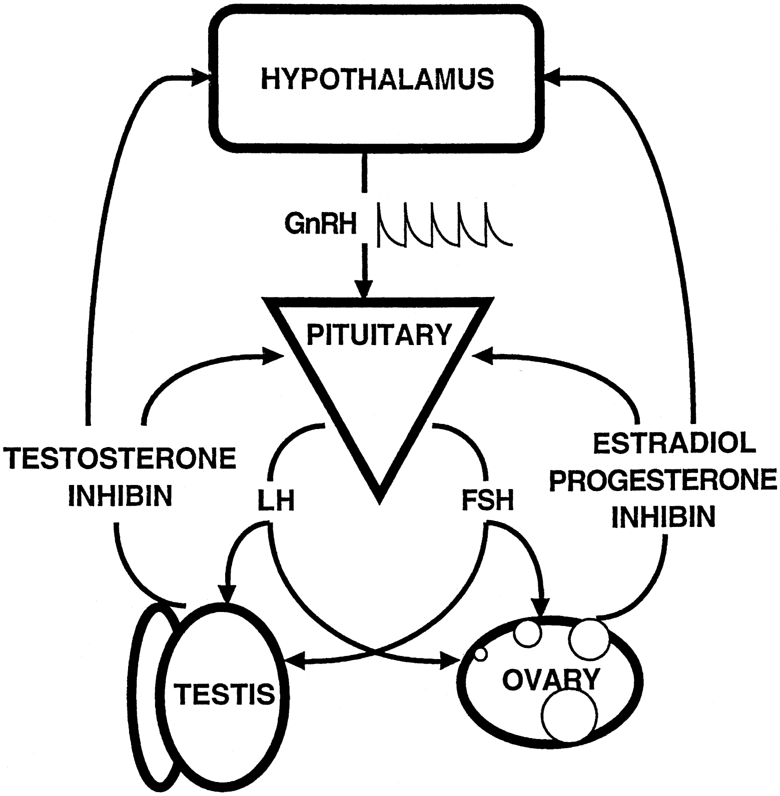

FIGURE 4-1 The hypothalamic-pituitary-gonadal axis (hypothalamic-pituitary-testicular axis in males, hypothalamic-pituitary-ovarian axis in females) and its principal hormones.

of the hypothalamus as the primary on-off switch controlling reproductive function.[18] The hypothalamus receives many inputs from other neural centers, allowing the discrete control of reproductive function to be susceptible to a broad range of influences. Olfactory, photoperiod, and tactile stimuli are known to modify hypothalamic function in many mammals. More complex influences on central nervous system activity may also be able to modify patterns of GnRH release and so affect reproductive function. However, hypothalamic control of HPG axis activity is primarily discrete and qualitative. Quantitative variation in the activity of the axis is regulated by steroid feedback and linkages to general metabolism.

The pituitary responds to GnRH from the hypothalamus by synthesizing and releasing FSH and LH. These hormones are also released in a pulsatile fashion in adults, although the pattern of gonadotropin secretion does not directly reflect the pattern of GnRH secretion. In women in particular, the frequency and amplitude of gonadotropin pulses is greatly modified by the levels of circulating steroid hormones.[19,20]

The testes and ovaries respond to stimulation by the gonadotropins in broadly analogous ways. In the testis, LH stimulates production of testosterone by the Leydig cells clustered outside the basement membrane that surrounds the seminiferous tubules. FSH stimulates the Sertoli cells inside the tubules. The Sertoli cells respond by nurturing the development of the spermatocytes as well as by secreting a protein hormone, inhibin, that differentially suppresses pituitary production of FSH. Testosterone also stimulates Sertoli function while suppressing pituitary release of both gonadotropins. As a result of these feedback controls, gamete production in a normal man is self-sustaining, with gonadotropins maintained at a low level. Interruptions of gamete production, however, are followed by rises in the gonadotropins that reinitiate the process.[21]

In the ovary, LH stimulates testosterone production by the cells clustered around the outside of the basement membrane surrounding a developing follicle. FSH stimulates the granulosa cells inside the follicle to convert testosterone to estradiol and support the development of the oocyte. The granulosa cells also secrete inhibin with a suppressive effect on FSH. After ovulation, the follicle is transformed into a corpus luteum, secreting progesterone and inhibin. Among the important peripheral targets for ovarian steroids is the endometrial lining of the uterus. Estradiol production in the follicular phase of the menstrual cycle stimulates endometrial proliferation. Progesterone production in the luteal phase following ovulation stimulates secretory activity by the endometrium and maintains its viability. In the absence of progesterone, a developed endometrium will soon be sloughed off in menstruation. Menstrual blood loss thus implies estradiol production but not necessarily progesterone production. Nor, by extension, does menstruation necessarily imply ovulation.[22]

The combined effect on the pituitary of steroid and inhibin production by the gonads is primarily inhibitory. Gonadectomy in either sex and menopause in women are characterized by high and unrestrained levels of pituitary gonadotropins. In men, the HPG axis normally functions at a sustained level, although acute variations as well as age-related changes occur. In women, the waves of follicular maturation that characterize ovarian cycles cause cyclic variation in both ovarian and pituitary hormones. The interaction of ovarian and pituitary signals is elegantly designed to produce key events of the ovarian cycle, such as the selection of the dominant follicle and ovulation.

Gonadal function is also subject to regulation by factors outside the HPG axis. Several major regulators of metabolism affect gonadal function, including insulin, cortisol, growth hormone, and insulinlike growth factor-1 (IGF-I).[23,24] In addition, the adrenal cortex represents a significant source of steroid production that is not under the control of the HPG axis but may nevertheless affect its activity. These sources of regulation are likely to have quantitative effects on the activity of the HPG axis rather than discrete, qualitative effects.

Maturation of the HPG Axis

The feedback relationships governing the HPG axis become established during gestation. After birth, the withdrawal of placental steroids results in a period of high gonadotropin secretion in the neonate. Over a period of months, the sensitivity of the axis to negative feedback appears to increase, leading to a decline in gonadotropin secretion to the very low levels characteristic of early childhood.[25,26] Pulsatile gonadotropin secretion is observable in prepubertal children but at very low amplitudes. Pulse frequency in prepubertal boys is comparable to that in adults while the frequency observed in girls is considerably slower.[27] The first evidence of a change in HPG axis activity is the appearance of sleep-associated increased LH pulse amplitude in both sexes and an associated increase in pulse frequency in girls, occurring in girls about 8–9 years old and in boys 1–2 years later.[28,29] Changes in FSH activity also are likely during this period but are more difficult to document, given the lower circulating levels of FSH than LH. Over time, the pulsatile pattern of LH secretion extends to characterize the entire 24-hour period.

These early elevations of gonadotropins are associated with gonadal maturation in both sexes. Testis volume begins to increase from childhood values of some 2 ml to adult values of 12–25 ml. This increase is associated with growth of the seminiferous tubules, appearance of Sertoli cells, and proliferation of spermatocytes. Pulsatile LH secretion leads to Leydig cell stimulation and increases in circulating testosterone levels. Rising testosterone levels stimulate a host of other pubertal changes, including the appearance of pubic, axillary, and facial hair, voice changes, accelerated linear growth, and increases in muscle mass. The differential responsiveness of these target tissues to androgenic stimulation is largely responsible for the variations in timing of these pubertal changes among individuals.[30–32]

In girls ovarian growth occurs throughout childhood.[33] Increased LH stimulation at the beginning of puberty leads to increases in ovarian steroid production, with estradiol levels approaching those characteristic of women in the follicular phase.[34] Testosterone levels also rise and the ratio of testosterone to estradiol is somewhat higher in puberty than adulthood.[35] The development of pubic and axillary hair, breast enlargement, linear growth acceleration, pelvic remodeling, and increases in adiposity are all characteristic consequences of increasing steroid production.[32] The first appearance of menstrual bleeding, known as *menarche*, is also a reflection of increasing estradiol levels. It tokens a level of estrogenic stimulation sufficient to cause endometrial proliferation. Although the first menstrual period is a discrete event in the life of an individual, it should be noted that is merely the first outward manifestation of a continuously changing level of endometrial stimulation.

The ability of the gonads to produce gametes also matures during the pubertal period. In boys, the first appearance of sperm in urine occurs in association with the early increases in gonadotropin secretion, but regular sperm production is not established until several years later.[36] In girls, ovulation is extremely unlikely before menarche and may lag behind menarche by many months. Both longitudinal and cross-sectional studies indicate that the frequency of ovulation increases steadily after menarche and may not reach adult rates for many years.[37] In men, androgen levels reach a peak by the late teens to early twenties, at about the time that linear growth is completed. In women, gonadal steroid levels and frequencies of ovulation may continue to increase for several years after the cessation of linear growth, accompanied by continuing changes in body composition.

LH Surge in Females

It is often claimed that the maturation of the HPO axis in females includes the development of a positive feedback response to estradiol as part of the mechanism of ovulation.[38,39] This conclusion derives from the fact that an LH surge can be elicited in mature women by supplying large increments of exogenous estradiol, whereas the same response cannot be elicited in prepubertal girls. However, the mechanism of positive feedback itself and its role in stimulating the normal midcycle LH surge has recently been challenged. Levran et al.[40] demonstrated that the LH surge in mature women is a consequence of a leveling-off or decline in estradiol levels after a preceding rise and is not triggered by the attainment of any threshold level of estradiol. They argue that the withdrawal of the negative feedback of estradiol on LH release precipitates the dramatic surge of accumulated gonadotropins and that it is not necessary to postulate a separate positive feedback mechanism. Notably, however, to effectively produce an LH surge, a drop in estradiol must follow a sustained rise and must also occur in an individual with adult levels of baseline LH production. The reason why an LH surge is not produced in a prepubertal girl by the same estradiol treatment that is effective in an adult, in this view, is that baseline LH production is too low for appreciable amounts to accumulate in the releasable pool. Hence, the appearance of the LH surge late in female puberty does not necessarily token the initiation of a new, positive feedback relationship.

CAUSES AND CORRELATES OF HPG AXIS MATURATION

Early experiments involving transplants of pituitary and gonadal tissue between immature and mature animals led to the conclusion that changes in hypothalamic function must be responsible for pubertal activation of the HPG axis.[41] This conclusion has been elegantly confirmed by experiments on immature rhesus monkeys where exogenous administration of pulsatile GnRH led to rapid and premature establishment of adult HPG axis function.[42] Humans who lack endogenous capacity for GnRH production ordinarily fail to undergo normal pubertal development but can be induced to do so through exogenous administration of pulsatile GnRH.[17] Conversely, precocious puberty can be caused by premature appearance of a pulsatile GnRH pattern and can often be arrested by exogenous administration of long-acting GnRH agonists that swamp the endogenous pulsatile signal.[43,44] Thus, puberty does not seem to be limited by the maturational status of either the pituitary or the gonad. Rather it is assumed that some process leads to the establishment of a mature pattern of circhoral GnRH production by the hypothalamus. The elucidation of this process represents a continuing challenge. Controversy exists both over the nature of the functional change that occurs in the hypothalamus and the factors that cause the change.

Two leading hypotheses have been advanced to describe the functional changes in the HPG axis at puberty. According to the first, initially applied to humans by Kulin, Grumbach, and Kaplan,[45] a decrease in the sensitivity of the hypothalamus to the negative feedback effects of gonadal steroids occurs in puberty, leading to a progressive rise in the circulating levels of gonadotropins and steroids. This hypothesis has been referred to as the *gonadostat hypothesis*, evoking an analogy between the HPG axis and the thermostat regulating heat production by a furnace. Puberty, in this analogy, is caused by a resetting of the "gonadostat" to a higher level, so that more circulating steroid is necessary to turn off the flow of gonadotropins, in the same way that setting a thermostat higher requires more heat to turn off the stimulating signal to the furnace. Support for this hypothesis comes from demonstrations of the suppression of gonadotropin levels in prepubertal children by low levels of exogenous steroids that are ineffective in adults.

Plant[27] criticized this hypothesis and suggested an alternative based on changes in the positive stimulation of gonadotropin production. He noted that the gonadostat hypothesis implies that the castration of a prepubertal individual should lead to a dramatic rise in gonadotropins, a phenomenon that does not, in fact, occur. Instead, prepubertal castration of male or female rhesus monkeys leads to only small increases in gonadotropin levels, much smaller than observed following the castration of adult animals. Rather than being held in check by an extreme sensitivity to the low, prepubertal levels of circulating steroids, Plant argued that gonadotropin production in the prepubertal animal is subject to weak positive stimulation. Puberty, in his view, results from an increase in this positive "hypophysiotropic drive."

Neither of these hypotheses resolves the issue of the proximate causes of HPG axis maturation. It is suspected that changes in neurotransmitter or neuromodulator activity are involved in the maturational changes of the hypothalamus,[46] but whether these changes arise on an endogenous developmental schedule or are coupled to other somatic or endocrine maturational events remains an area of ongoing investigation. In considering this question, it is important to adequately distinguish potential causes of HPG axis maturation from correlated and consequent events.

Adrenarche

Humans share with the other African apes a characteristic of adrenal development known as *adrenarche*, which usually precedes recognizable pubertal changes in the HPG axis by 1 or 2 years.[2,47–49] During this period, the adrenal cortex acquires a third secretory zone, the zona reticularis, functionally analogous to the zona fetalis of the fetal adrenal (Figure 4-2). During gestation, the zona fetalis produces androgens that serve as precursors for placental estrogen synthesis. Like the zona fetalis, the zona reticularis produces large quantities of the C-19 steroid hormones dehydroepiandrosterone (DHEA) and androstenedione (A). Circulating levels of these hormones rise in prepubertal children, together with levels of their sulfate conjugates, before detectable increases in gonadotropins and gonadal steroids. These adrenal androgens have weak potency at androgen receptors and may also serve as substrates for conversion to estrogens in peripheral tissues and the hypothalamus itself. It has been suggested by some that adrenal androgens may contribute to the maturation of the HPG axis, perhaps by desensitizing the hypothalamus through exposure to rising steroid levels outside its own regulatory control.[50]

The potential for adrenal androgen production to influence pubertal development is most clearly demonstrated in cases of untreated congenital adrenal hyperplasia.[51,52] Uncontrolled overproduction of adrenal androgens in childhood, which can result from specific enzyme deficiencies, can precipitate precocious puberty, including HPG axis activation, in both boys and girls. Whether adrenarche has a significant influence on the timing or pace of puberty in nonpathological situations is less clear. Some data suggest that early adrenarche is associated with an advancement of subsequent pubertal events within the normal range of variation.[53] The relationship may be stronger in girls, where adrenal androgen levels may contribute significantly to the adolescent growth spurt and to the development of pubic hair.

The factors that control the timing of adrenarche remain obscure, however. There is no evidence of a rise in pituitary adrenocorticotropic hormone levels and no concomitant rise in cortisol production at the time of adrenarche. Increased androgen production involves alteration in the enzyme activity of the steroid synthetic pathway, including a suppression of 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) and an induction of 17,20-lyase activity.[54,55] Estradiol has been shown to have a suppressive effect on 3-beta HSD, and girls with precocious adrenarche have been

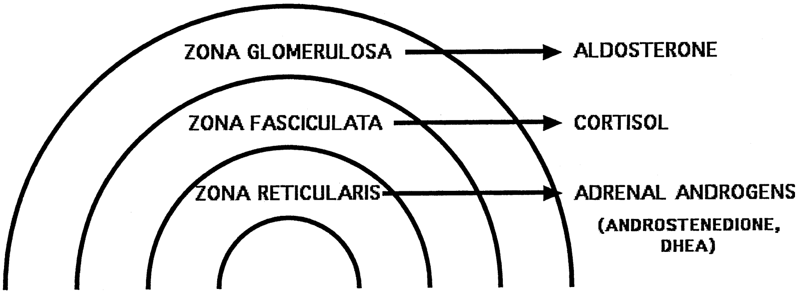

FIGURE 4-2 The layers of the adult adrenal cortex and the principal steroids produced by each layer.

observed to have elevated estradiol levels. These observations led some to suggest that as yet undetectable increases in ovarian estradiol production early in puberty may trigger adrenarche in girls.[56] This possibility has not yet been discriminated from the alternative, that elevated estradiol is a consequence and not a cause of precocious adrenarche, nor does it provide an explanation of the timing of adrenal development in boys. Insulinlike growth factor I has also been observed to induce 17,20-lyase activity and promote adrenal androgen production in both the zona fetalis and the zona reticularis, and insulin sensitivity has been observed to be negatively correlated with adrenal androgen production by the zona reticularis.[57,58] Therefore, it may be that developmental changes in either the somatotropic axis or insulin sensitivity in late childhood play a role in initiating adrenarche in both sexes.

Somatotropic Axis

The somatotropic axis exerts pronounced effects on the proliferation and maintenance of many tissues, including the stimulation of skeletal growth and protein anabolism. Both stimulatory and inhibitory hormones are secreted by the hypothalamus into the hypophyseal portal system, where they control the release of growth hormone (GH) from the anterior pituitary. GH is secreted in a pulsatile fashion, much like the gonadotropins. Although GH has direct effects on some cells, many of its effects are mediated by the local production of insulinlike growth factors (IGFs) in target tissues.

Increased activity of the somatotropic axis is a normal part of pubertal development, stimulating both the linear acceleration in skeletal growth and the accumulation of lean body mass.[59,60] The increase in somatotropic axis activity appears to be a consequence of increased gonadal steroid production.[61–63] Both estradiol and testosterone affect GH production by augmenting GH pulse amplitude, although testosterone may achieve this effect after aromatization to estradiol within the hypothalamus. Increases in IGF-I, the major mediator of GH action on skeletal growth, are correlated with Tanner stages of pubertal development and gonadal steroid levels. GH and IGF-I also have stimulatory effects on gonadal steroid production, and gonadal steroids have independent effects on skeletal growth not mediated by the somatotropic axis.[24,64–66] Thus, the somatotropic axis and the HPG axis function synergistically in promoting the adolescent growth spurt. The initial stimulation, however, comes from maturation of the HPG axis.

Insulin Sensitivity

Insulin levels rise during puberty as a consequence of a transient decrease in insulin sensitivity.[67,68] In euglycemic clamp studies, the insulin response to a glucose challenge is observed to be two- to threefold greater during puberty than in either prepubescent children or postpubescent adults.[69] The change in insulin sensitivity is closely correlated with Tanner stages of pubertal development, decreasing simultaneously with the initiation of pubertal development (Tanner stage 2) and returning to normal by the end of puberty (Tanner stage 5). The pubertal decrease in insulin sensitivity is also closely correlated with increases in GH and body mass index (BMI), even after correction for sex, age, and pubertal stage.[70] Increases in GH may contribute to decreases in insulin sensitivity by increasing the rate of glucose uptake by anabolic tissues, but increased insulin levels may potentiate GH effects as well. Insulin has a suppressive effect on IGF-binding proteins, thus raising free levels of IGF-1.[68] Insulin has also been shown to increase gonadotropin-stimulated gonadal steroid production in the ovary.[23,69] Hyperinsulinemic states are often associated with advanced pubertal progression while hypoinsulinemic states are often associated with pubertal delay. Whether developmental changes in insulin resistance independently contribute to normal HPG axis maturation via effects on gonadal steroid production has not been thoroughly explored.

Body Composition

Frisch and colleagues suggested, in the 1970s, that changes in body composition had an important causal influence on HPO axis maturation in females.[71,72] Although it has been extensively criticized on empirical and theoretical grounds (see the review in Ellison[73]), this hypothesis continues to be widely cited. Significant changes in body composition occur during puberty in both sexes, with males increasing in lean body mass percentage and females increasing in fat mass percentage. In both cases, however, these changes are consequences of increased production of gonadal steroids rather than causes or even antecedents.[74] Longitudinal studies of pubertal maturation in girls have clearly documented that increases in gonadal estrogen production precede any change in body composition, with significant increases in fat percentage occurring after menarche.[75,76] In boys, the increases in muscle mass that accompany puberty are direct consequences of the anabolic effects of gonadal testosterone.[77] Thus, in both sexes, changes in body composition must be viewed as downstream consequences of the maturation of the HPG axis and not contributing causes.

Leptin

Considerable confusion and controversy surrounds the role of leptin in human physiology generally and pubertal development in particular.[78–82] Leptin is a 16-KDa cytokine of the tumor necrosis factor group coded by the ob gene. In rodents, leptin appears to affect hypothalamic centers, regulating food intake and energy expenditure. Deficiency in either leptin (ob mutants) or its receptor (db mutants) leads to hyperphagia and inactivity. Exogenous leptin administration in ob mutants leads to reductions in food intake and increases in energy expenditure.[83] In humans, defects in leptin signaling (both leptin deficiency and leptin receptor defects) have also been associated with massive, early onset obesity.[84,85] However, administration of exogenous leptin to human subjects has no significant effect on weight change, energy intake, or energy expenditure.[86] Thus, the relationship of leptin to energy metabolism appears to be different in rodents and humans.[87]

In humans, leptin is primarily produced in adipocytes of subcutaneous fat tissue.[88] Leptin receptors occur in the hypothalamus, although not on GnRH-producing cells, and in various peripheral tissues, including the ovary.[89,90] In adults, circulating levels of leptin are positively correlated with fat mass. The relationship is highly sexually dimorphic, however, with women typically having threefold higher leptin levels per fat mass than men. This dimorphism is a result of the effects of gonadal steroids, testosterone suppressing, and estradiol enhancing leptin production.[74,91] In addition to fat mass and gender, leptin levels reflect energy balance and energy flux. Weight loss is associated with low levels of leptin per fat mass, and weight gain with high levels. Maintenance of a lower than normal weight through caloric intake restriction is also associated with low leptin levels per fat mass, indicating a suppressive effect of low energy flux.[92,93]

The effects of energy balance and energy flux on leptin levels may reflect the control of leptin production by factors regulating energy metabolism.[94,95] The control of leptin production by insulin has been particularly well demonstrated by recent studies. Leptin levels are more strongly correlated with insulin levels than with adiposity.[96,97] Children with new-onset type I (insulin-deficiency) diabetes have abnormally low leptin levels for their fat mass, but those levels quickly rise to the normal range with insulin therapy.[98] Similarly, biliopancreatic diversion in obese subjects produces a reduction in both insulin and leptin levels and a dissociation between leptin and fat mass.[99] The regulation of leptin production by insulin may underlie the relationship with energy balance and energy flux and may also contribute to reported population differences in leptin levels scaled for fat mass.[100–102]

In women, the stimulatory effect of estradiol on leptin production produces menstrual cycle variation in leptin levels and decreases in leptin production per fat mass in postmenopausal women.[74,103,104] Since ovarian function is known to respond to changes in energy balance, variation in ovarian steroid production may contribute to the relationship between energy balance and leptin production, a relationship somewhat stronger in women than men.[92]

In addition to defects in metabolic regulation, ob mutant mice are infertile with subnormal gonadotropin levels. Administration of leptin not only leads to weight reduction in these animals but raises gonadotropin levels and restores fertility.[105] These observations suggested a potential relationship between leptin and the HPG axis. It has been hypothesized that leptin levels may also trigger puberty in rodents. In mice, ob mutant females normally fail to undergo puberty but do so if treated with exogenous leptin. Wild-type female mice injected prepubertally with leptin grow more slowly but display vaginal opening and estrus behavior earlier than untreated controls.[106] In rats, leptin administration only partially reverses the delay in pubertal maturation caused by food restriction, leading to the suggestion that leptin levels may have a permissive, rather than a triggering, effect on puberty in that species.[107] In rhesus monkeys, there is no increase in leptin preceding the initiation of HPG axis maturation, leading to further doubt regarding the generalizability of the rodent model.[108]

There has been speculation that leptin may in some way contribute to the control of puberty in humans as well. Clinical evidence on this issue is somewhat ambiguous but on the whole does not support a direct effect of leptin on the timing of human puberty. Genetic mutations in leptin and its receptor have each been associated in human subjects with massive obesity and the failure of normal pubertal progression.[84,85] However, profound alterations of metabolism and pituitary function, including defects in growth hormone and thyrotropin production, also occur in these individuals, making the role of leptin in the failure of pubertal maturation uncertain. Precocious maturation of the HPG axis, on the other hand, is not associated with any change in leptin levels.[109,110] Andrelli et al.[111] report on two female patients, both of whom experienced complete atrophy of subcutaneous and visceral adipose tissue that occurred during childhood. Leptin levels in both women were well below the normal range, yet both experienced menarche between 11 and 12 years of age with regular menstrual cycles thereafter. Gonadotropin and gonadal steroid levels were normal for both women, one of whom had been pregnant and given birth three times.

Longitudinal and cross-sectional studies of leptin levels during puberty indicate a sustained increase in leptin levels in girls in association with increasing adiposity.[112–114] As noted previously, however, the increase in female adiposity is primarily a consequence of HPG axis maturation, not a cause. Hence, the pubertal increase in leptin production, correlated with the increases in fat mass, must be seen as a pubertal consequence as well. Sexual dimorphism in leptin production also develops during puberty but similarly is best understood as a downstream consequence of gonadal steroid production. In boys, early puberty is marked by a transient rise in leptin levels, which then decline to prepubertal levels as puberty progresses.[115,116] The transient rise may well be a consequence of the transient rise in insulin levels, which occurs at the same time, with the subsequent decline in leptin resulting both from a decline in insulin and a rise in testosterone.

In summary, there is little evidence that an elevation in leptin is either necessary or sufficient for the initiation of HPG axis maturation in humans. Pubertal changes in leptin concentrations are instead most easily understood as consequences of gonadal activity and insulin production. Rather than playing an important role in regulating reproductive maturation or mature reproductive function, leptin appears to be more closely associated with metabolic regulation and insulin dynamics in particular.

Skeletal Maturation

While the proximate causes of the initiation of pubertal maturation remain obscure, the synchronization of reproductive and physical maturation in humans is striking. Gonadal steroid production plays an important role in the accelerating and decelerating phases of the adolescent growth spurt, with androgens more important in the acceleration phase and estrogens more important in the deceleration phase.[117] Estrogen receptor defects can be associated with prolongation of the acceleration phase even in men.[118] It has been noted that in females variation in skeletal maturity and height decreases as menarche is approached with a close correlation between menarche and the attainment of adult pelvic dimensions.[119–121] The correlation between age at menarche and the attainment of adult pelvic size is demonstrable both within and between populations. Pelvic remodeling and the enlargement of the female birth canal are among the last events in skeletal growth and maturation, occurring as a consequence of gonadal estrogen production.[122] Because early and late-maturing women converge on similar adult internal pelvic dimensions, it has been suggested that the timing of puberty is coordinated to ensure the attainment of an appropriate physical scale for successful reproduction.[73,120] This perspective recognizes that physical constraints on successful female reproduction must be overcome before energetic constraints become salient. Therefore, it would make sense, from an adaptive perspective, for the timing of reproductive maturation to be conditioned on signals related to overall size and for shifts in metabolic energy allocation (such as increasing fat storage) to be consequences of puberty rather than causes.

The association of puberty with skeletal growth and maturation is also reflected in the close correlation between secular trends in height and age at menarche.[123] Considerable evidence now documents the historical trend toward increasing height and decreasing menarcheal age in northern and western European populations during the nineteenth and twentieth centuries. Both height at menarche and final adult height in women increased during this period while weight for height at menarche declined. The advance in pubertal timing thus seems to have been correlated with accelerated skeletal development, not with accelerated accumulation of adipose tissue.

END OF PUBERTY

The completion of pubertal development receives much less attention than its initiation. Conventionally, the pubertal phase of development is considered to end with the attainment of final adult height. There is considerable evidence that ovarian function continues to mature in women, however, long after this point.[37,124–126] The frequency of ovulation and levels of gonadal hormones continue to rise in European and American women until the early to midtwenties. There is also evidence that the tempo of this later phase of reproductive maturation is correlated with the tempo of earlier maturation, so that women with late menarcheal ages take longer after menarche to attain their fully mature levels of ovarian function.[37,127] This late phase of reproductive maturation in women is also associated with ovulation from smaller follicles and lower levels of fecundity.[128] Although males typically take longer to initiate puberty and reach final adult height, there does not appear to be as prolonged a phase of reproductive maturation after adult height is attained. Adult sperm counts and concentrations are usually attained by that time and testosterone levels and muscle mass peak soon after. Whether the later phase of female reproductive maturation is properly understood as a part of pubertal development or as a different trajectory of adult reproductive function deserves fuller consideration.

CONCLUSION

Puberty, the process of reproductive maturation, is primarily a process of neuroendocrine maturation of the HPG axis. Some of the principal hormones of puberty and their relationships with each other and with parameters of physical maturation are summarized in Figure 4-3. After a long period of functional quiescence, the hypothalamus begins to secrete GnRH in an adult, pulsatile pattern, leading to increased production of pituitary gonadotropins, which in turn stimulate gonadal production of steroid hormones and gametes. Increasing gonadal steroid production leads to a broad array of developmental effects, including the stimulation of the adolescent growth spurt, the development of secondary sex characteristics, and sexual dimorphism in body composition and leptin production. The mechanisms that initially stimulate this reawakening of the HPG axis remain obscure but may normally be linked to signals reflecting physical size and skeletal maturity. In women, reproductive maturation, reflected in increasing indices of ovarian function and fecundity, continues for several years after the attainment of final adult height, while in men, reproductive maturation is largely complete at that time.

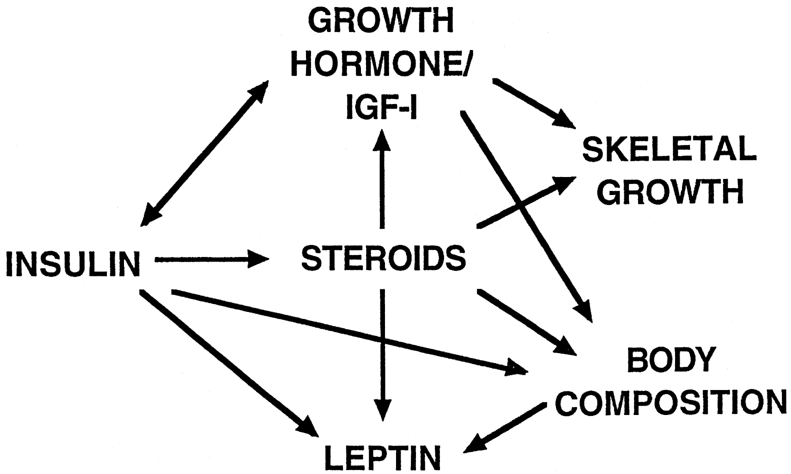

FIGURE 4-3 Some of the principal hormones of human puberty reviewed in the text and their regulatory effects on each other and on the principal parameters of physical maturation.

SUGGESTED READING

The following sources provide excellent coverage of the physiology of human puberty from a variety of perspectives and can be used to supplement the references cited in the text.

Hormone Research, Vol. 51, Suppl 3 (1999), contains a number of review articles covering the latest research on human puberty emphasizing pathologies and their treatment.

Yen SSC, Jaffe RB, Barbieri RL (eds). Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management, 4th ed., Philadelphia: Saunders, 1999. The latest edition of one of the standard reference works on reproductive physiology. Comprehensive yet accessible, there are excellent chapters on normal puberty and disorders of development.

Knobil E, Neill JD (eds). The Physiology of Reproduction, 2nd ed., New York: Raven Press, 1994. The most comprehensive work on reproductive physiology available, with excellent chapters on the HPG axis and its maturation.

Wood JW. Dynamics of Human Reproduction: Biology, Biometry, and Demography. New York: Aldine, de Gruyter, 1994. Includes a discussion of human puberty that stresses a demographic perspective.

Ellison PT. On Fertile Ground: Ecology, Evolution, and Human Reproduction. Cambridge, MA: Harvard University Press, 2001. Covers the physiology of human reproduction, including puberty, from an evolutionary and ecological perspective and is written for a general audience.

Donovan BT, Van der Werff ten Bosch JJ. Physiology of Puberty. London: Edward Arnold, 1965. A classic work that reviews the important historical experiments that contributed to the modern understanding of the role of the HPG axis in pubertal maturation.

REFERENCES

1. Paige KE, Paige JM. The Politics of Reproductive Ritual. Berkeley: University of California Press, 1981.
2. Sizonenko PC. Physiology of puberty. J Endocrinol Invest. 1989;12(Suppl 3):59–63.
3. Styne DM. Physiology of puberty. Horm Res. 1994;41(Suppl 2):3–6.
4. Apter D. Development of the hypothalamic-pituitary-ovarian axis. Ann NY Acad Sci. 1997;816:9–21.
5. Brook CG. Mechanism of puberty. Horm Res. 1999;51(Suppl 3):52–54.
6. Matsuo H, Babba Y, Nair RMG, Arimura A, Schaly AV. Structure of the porcine LH- and FSH-releasing hormone. I. The proposed amino acid sequence. Biochem Biophys Res Commun. 1971;43:1334–1339.
7. Burgus R, Butcher M, Ling N, Monahan M, Rivier J, Fellows R, et al. Structure moléculaire du facteur hypothalamique (LRF) d'origine ovine contrôlant la sécrétion de l'hormone gonadotrope hypophysaire de lutínisation. CR Acad Sci [Paris]. 1971;273:1611–1613.
8. Krey LC, Butler WR, Knobil E. Surgical disconnection of the medial basal hypothalamus and pituitary function in the rhesus monkey. Endocrinol. 1975;96:1073–1087.

9. Carmel PW, Araki S, Ferin M. Pituitary stalk portal blood collection in rhesus monkeys: Evidence for pulsatile release of GnRH. Endocrinol. 1976;99:243–248.
10. Neill JD, Patton JM, Dailey RA, Tsou RC, Tindall GT. Luteinizing hormone releasing hormone (LHRH) in pituitary portal blood of rhesus monkeys: Relationship to level of LH release. Endocrinol. 1977;101:430–434.
11. Plant TM, Krey LC, Moossy J, McCormack JT, Hess DL, Knobil E. The arcuate nucleus and the control of gonadotropin and prolactin secretion in the female rhesus monkey (Macaca mulatta). Endocrinol. 1978;102:52–62.
12. Belchetz P, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophyseal responses to continuous and intermittent delivery of hypothalamic gonadotropin releasing hormone. Science. 1978;202:631–633.
13. Wildt L, Hausler A, Marshall G, Hutchinson JS, Plant TM, Belchetz PE, et al. Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. Endocrinol. 1981;109:376–385.
14. Crowley WF Jr, McArthur J. Stimulation of the normal menstrual cycle in Kallmann's syndrome by pulsatile administration of luteinizing hormone-releasing hormone (LHRH). J Clin Endocrinol Metab. 1980;51:173–175.
15. Norman RL, Gliessman P, Lindstrom SA, Hill J, Spies HG. Reinitiation of ovulatory cycles in pituitary stalk-sectioned monkeys: Evidence for a specific hypothalamic message for the preovulatory release of luteinizing hormone. Endocrinol. 1982;111:1874–1882.
16. Hurley DM, Brian R, Outch K, Stockdale J, Fry A, Hackman C, et al. Induction of ovulation and fertility in amenorrheic women by pulsatile low-dose gonadotropin-releasing hormone. N Engl J Med. 1984;310:1069–1074.
17. Santoro N, Filicori M, Crowley WF Jr. Hypogonadotropic disorders in men and women: Diagnosis and therapy with pulsatile gonadotropin-releasing hormone. Endocrinol Rev. 1986;7:11–23.
18. Knobil E, Plant TM, Wildt L, Belchetz PE, Marchall G. Neuroendocrine control of the rhesus monkey menstrual cycle: Permissive role of the hypothalamic gonadotropin-releasing hormone (GnRH). Science. 1980;207:1371–1373.
19. Knobil E. Patterns of hypophysiotrophic signals and gonadotropin secretion in the rhesus monkey. Biol Reprod. 1981;24:44–49.
20. Veldhuis JD, Beitins IZ, Johnson ML, Serabian MA, Dufau ML. Biologically active luteinizing hormone is secreted in episodic pulsations that vary in relation to the stage of the menstrual cycle. J Clin Endocrinol Metab. 1984;58:1050–1058.
21. Hall PF. Testicular steroid synthesis: organization and regulation. In: Knobil E, Neill JD (eds). The Physiology of Reproduction. New York: Raven Press, 1988:975–998.
22. Yen SSC. The human menstrual cycle: Neuroendocrine regulation. In: Yen SSC, Jaffe RB (eds). Reproductive Endocrinology, 3rd ed. Philadelphia: Saunders, 1991:273–308.
23. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocrinol Rev. 1987;8:132–141.
24. Adashi EY, Resnick CE, Hurwitz A, Ricciarelli E, Hernandez ER, Roberts CT, et al. Insulin-like growth factors: the ovarian connection. Hum Reprod. 1991;6:1213–1219.
25. Winter JSD, Faiman C, Hobson WC, Prasad AV, Reyes FI. Pituitary-gonadal relations in infancy. I. Patterns of serum gonadotropin concentrations from birth to four years of age in man and chimpanzee. J Clin Endocrinol Metab. 1975;44:1130–1141.
26. Kaplan SL, Grumbach MM, Aubert ML. The ontogenesis of pituitary hormones and hypothalamic factors in the human fetus: Maturation of central nervous system regulation of anterior pituitary function. Recent Progr Horm Res. 1976;32:161–234.
27. Plant TM. Puberty in primates. In: Knobil E, Neill JD (eds). The Physiology of Reproduction. New York: Raven Press, 1988:1763–1788.
28. Boyar R, Perlow M, Kapen S, Hellman L, Weitzman ED. Twenty-four hour patterns of luteinizing hormone secretions in normal men with sleep stage recording. J Clin Endocrinol Metab. 1972;35:73–81.
29. Boyar RM. Control of the onset of puberty. Ann Rev Med. 1978;29:509–520.
30. August GP, Grumbach MM, Kaplan SJ. Hormonal changes in puberty: III. Correlation of plasma testosterone, LH, FSH, testicular size, and bone age with male pubertal development. J Clin Endocrinol Metab. 1972;34:319–326.

31. Winter JSD, Faiman C. Pituitary-gonadal relations in male children and adolescents. Pediatr Res. 1972;6:126–135.
32. Marshall WA. Puberty. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 2. Postnatal Growth. New York: Plenum, 1978:141–181.
33. Peters H, Himelstein-Braw R, Faber M. The normal development of the ovary in childhood. Acta Endocrinol. 1976;82:617–630.
34. Winter JSD, Faiman C. Pituitary-gonadal relations in female children and adolescents. Pediatr Res. 1973;7:948–953.
35. Apter D, Vihko R. Serum sex hormone-binding globulin and sex steroids in relation to pubertal and postpubertal development of the menstrual cycle. Prog Reprod Biol Med. 1990;14:58–69.
36. Neilsen CT, Skakkebak NE, Richardson DW, Darling JAB, Hunter WM, Nielsen A, et al. Onset of the release of spermatozoa (spermarche) in boys in relation to age, testicular growth, pubic hair and height. J Clin Endocrinol Metab. 1986;62:532–535.
37. Apter D, Vihko R. Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. J Clin Endocrinol Metab. 1983;57:82–86.
38. Reiter EO, Kulin HE, Hamwood SM. The absence of positive feedback between estrogen and luteinizing hormone in sexually immature girls. Pediatr Res. 1974;8:740–745.
39. Presi J, Horejsi J, Stroufova A, Herzmann J. Sexual maturation in girls and the development of estrogen-induced gonadotropic hormone release. Ann Bio Anim Biochem Biophys. 1976;16:377–383.
40. Levran D, Ben-Shlomo I, Luski A, Ben-Rafael Z, Dor J, Mashiach S, et al. A reappraisal of the feedback effects of oestradiol upon luteinizing hormone surge. Hum Reprod. 1995;10: 3117–3130.
41. Donovan BT, Van der Werff ten Bosch JJ. Physiology of Puberty. London: Edward Arnold, 1965.
42. Wildt L, Marshall G, Knobil E. Experimental induction of puberty in the infantile female rhesus monkey. Science. 1980;207:1373–1375.
43. Mansfield MJ, Beardsworth DE, Loughlin JS, Crawford JD, Bode HH, Rivier J, et al. Long-term treatment of central precocious puberty with long-acting analogue of luteinizing hormone releasing hormone. N Engl J Med. 1983;309:1286–1290.
44. Lee PA. Central precocious puberty. An overview of diagnosis, treatment, and outcome. Endocrinol Metab Clin North Amer. 1999;28:901–918.
45. Kulin HE, Grumbach MM, Kaplan SL. Changing sensitivity of the pubertal gonadal hypothalamic feedback mechanism in man. Science. 1969;166:1012–1013.
46. Veldhuis JD. Neuroendocrine mechanisms mediating awakening of the human gonadotropic axis in puberty. Pediatr Neurol. 1996;10:304–317.
47. Sizonenko PC. Endocrinology in preadolescents and adolescents. I. Hormonal changes during normal puberty. Am J Dis Child. 1978;132:704–712.
48. Cutler GB, Loriaux DL. Adrenarche and its relationship to the onset of puberty. Fed Proc. 1980;39:2384–2390.
49. Genazanni AR, Thijssen JH, Siiteri PK (eds). Adrenal Androgens. New York: Raven Press, 1980.
50. Siiteri PK. Obesity and peripheral estrogen synthesis. In: Frisch RE (ed). Adipose Tissue and Reproduction. Basel, Switzerland: Karger, 1990:70–84.
51. Bethune JE. The Adrenal Cortex. Kalamazoo, MI: Upjohn, 1974.
52. Styne DM, Grumbach MM. Disorders of puberty in the male and female. In: Yen SSC, Jaffe JB (eds). Reproductive Endocrinology, 3rd ed. Philadelphia: Saunders, 1991:511–554.
53. Pere A, Perheentupa J, Peter M, Voutilainen R. Follow up of growth and steroids in premature adrenarche. Eur J Pediatr. 1995;154:346–352.
54. Gell JS, Carr BR, Sasano H, Atkins B, Margraf L, Mason JI, et al. Adrenarche results from development of a 3-beta-hydroxysteroid dehydrogenase-deficient adrenal reticularis. J Clin Endocrinol Metab. 1998;83:3695–3701.
55. Miller WL. The molecular basis of premature adrenarche: An hypothesis. Acta Paediatr. 1999;Suppl 88:60–66.
56. Warne GL, Carter JN, Faiman C, Reyes FI, Winter JS. Hormonal changes in girls with precocious adrenarche: A possible role for estradiol or prolactin. J Pediatr. 1978;92:743–747.

57. Mesiano S, Katz SL, Lee JY, Jaffe RB. Insulin-like growth factors augment steroid production and expression of steroidogenic enzymes in human fetal adrenal cortical cells: Implications for adrenal androgen regulation. J Clin Endocrinol Metab. 1997;82:1390–1396.
58. Vuguin P, Linder B, Rosenfeld RG, Saenger P, DiMartino-Nardi J. The roles of insulin sensitivity, insulin-like growth factor I (IGF-I), and IGF-binding protein-1 and -3 in the hyperandrogenism of African-American and Caribbean Hispanic girls with premature adrenarche. J Clin Endocrinol Metab. 1999;84:2037–2042.
59. Martha PM, Reiter EO. Pubertal growth and growth hormone secretion. Endocrinol Metab Clin North Am. 1991;20:165–182.
60. Hartman ML, Iranmanesh A, Thorner MO, Veldhuis JD. Evaluation of pulsatile patterns of growth hormone release in humans: A brief review. Am J Hum Biol. 1993;5:603–614.
61. Brook CG, Hindmarsh PC. The somatotropic axis in puberty. Endocrinol Metab Clin North Am. 1992;21:767–782.
62. Loche S, Casini MR, Faedda A. The GH/IGF-I axis in puberty. Br J Clin Pract Symp. 1996;Suppl 85:1–4.
63. Caufriez A. The pubertal growth spurt: effects of sex steroids on growth hormone and insulin-like growth factor I. Eur J Obstet Gynecol Reprod Biol. 1997;71:215–217.
64. Lackey BR, Gray SL, Henricks DM. The insulin-like growth factor (IGF) system and gonadotropin regulation: Actions and interactions. Cytokine Growth Factor Rev. 1999;10:201–217.
65. Libanti C, Baylink DJ, Lois-Wenzel E, Srinvasan N, Mohan S. Studies on the potential mediators of skeletal changes occurring during puberty in girls. J Clin Endocrinol Metab. 1999;84:2807–2814.
66. Mauras N. Growth hormone, insulin-like growth factor I and sex hormones: Effects on protein and calcium metabolism. Acta Paediatr. 1999;Suppl 88:81–83.
67. Caprio S. Insulin: The other anabolic hormone of puberty. Acta Paediatr. 1999;Suppl 88:84–87.
68. Poretsky L, Cataldo NA, Rosenwaks Z, Giudice LC. The insulin-related ovarian regulatory system in health and disease. Endocr Rev. 1999;20:535–582.
69. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: Results from clamp studies in 357 children. Diabetes. 1999;48:2039–2044.
70. Acerini CL, Cheetham TD, Edge JA, Dunger DB. Both insulin sensitivity and insulin clearance in children with type I (insulin-dependent) diabetes vary with growth hormone concentrations and with age. Diabetologia. 2000;43:61–68.
71. Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of menarche. Arch Dis Child. 1971;46:695–701.
72. Frisch RE, McArthur JW. Menstrual cycles: Fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science. 1974;185:949–951.
73. Ellison PT. On Fertile Ground: Ecology, Evolution, and Human Reproduction. Cambridge, MA: Harvard University Press, 2001.
74. Rosenbaum M, Leibel RL. Role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin. J Endocrinol Metab. 1999;84:1784–1789.
75. de Ridder CM, Thijssen JHH, Bruning PF, Van den Brande JL, Zonderland ML, Erich WBM. Body fat mass, body fat distribution, and pubertal development: A longitudinal study of physical and hormonal sexual maturation of girls. J Clin Endocrinol Metab. 1992;75:442–446.
76. Legro RS, Lin HM, Demers LM, Lloyd T. Rapid maturation of the reproductive axis during perimenarche independent of body composition. J Clin Endocrinol Metab. 2000;85:1021–1025.
77. Round JM, Jones DA, Honour JW, Nevill AM. Hormonal factors in the development of differences in strength between boys and girls during adolescence: A longitudinal study. Ann Hum Biol. 1999;26:49–62.
78. Wurtman RJ. What is leptin for, and does it act on the brain? Nature Med. 1996;2:492–493.
79. Conway GS, Jacobs HS. Leptin: A hormone of reproduction. Hum Reprod. 1997;12:633–635.
80. Apter D. Leptin in puberty. Clin Endocrinol. 1997;47:175–176.
81. Flier JS. What's in a name? In search of leptin's physiologic role. J Clin Endocrinol Metab. 1998;83:1047–1413.

82. Rogol AD. Editorial: Leptin and puberty. J Clin Endocrinol Metab. 1998;83:1089–1090.
83. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science. 1995;269:540–543.
84. Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392:398–401.
85. Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. A leptin missense mutation associated with hypogonadism and morbid obesity. Nature Genet. 1998;18:213–215.
86. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, et al. Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. JAMA. 1999;282:1568–1575.
87. Himms-Hagen J. Physiological roles of the leptin endocrine system: Differences between mice and humans. Crit Rev Clin Lab Sci. 1999;36:575–655.
88. Roemmich JN, Rogol AD. Role of leptin during childhood growth and development. Endocrinol Metab Clin North Am. 1999;28:749–764.
89. Couce ME, Burguera B, Parisi JE, Jensen MD, Lloyd RV. Localization of leptin receptor in the human brain. Neuroendocrinol. 1997;66:145–150.
90. Karlson C, Lindell K, Svensson E, Bergh C, Lind P, Billig H, et al. Expression of functional leptin receptors in the human ovary. J Clin Endocrinol Metab. 1997;82:4144–4148.
91. Cassaibiell X, Piñeiro V, Peino R, Lage M, Camiña J, Gallego R, et al. Gender differences in both spontaneous and stimulated leptin secretion by human omental adipose tissue in vitro: Dexamethasone and estradiol stimulate leptin release in women, but not in men. J Clin Endocrinol Metab. 1998;83:2149–2155.
92. Rosenblum M, Nicolson M, Hirsch J, Murphy E, Chu F, Leibel RL. Effects of weight change on plasma leptin concentrations and energy expenditure. J Clin Endocrinol Metab. 1997;82:3647–3654.
93. Wadden TA, Considine RV, Foster GD, Anderson DA, Sarwer DB, Caro JS. Short- and long-term changes in serum leptin in dieting obese women: Effects of caloric restriction and weight loss. J Clin Endocrinol Metab. 1998;83:214–218.
94. Kolaczynski JW, Nyce MR, Considine RV, Boden G, Nolan JJ, Henry R. Acute and chronic effects of insulin on leptin production in humans: Studies in vivo and in vitro. Diabetes. 1996;5:699–701.
95. Larsson H, Ahren B. Short term dexamethasone treatment increases plasma leptin independently of changes in insulin sensitivity in healthy women. J Clin Endocrinol Metab. 1996;81:4428–4432.
96. Geisthövel F, Meysing A, Brabant G. C-peptide and insulin, but not C19-steroids, support predictive value of body mass index on leptin in serum of premenopausal women. Hum Reprod. 1998;13:547–553.
97. Carmina E, Ferin M, Gonzalez F, Lobo RA. Evidence that insulin and androgens may participate in the regulation of serum leptin levels in women. Fertil Steril. 1999;72:926–931.
98. Hanaki K, Becker DJ, Arslanian SA. Leptin before and after insulin therapy in children with new-onset type 1 diabetes. J Clin Endocrinol Metab. 1999;84:1524–1526.
99. de Marinis L, Mancini A, Bianchi VA, Milardi D, Proto A, Lanzone A, et al. Plasma leptin levels after biliopancreatic diversion: Dissociation with body mass index. J Clin Endocrinol Metab. 1999;84:2386–2389.
100. Luke AH, Rotimi CN, Cooper RS, Long AE, Forrester TE, Wilks R, et al. Leptin and body composition of Nigerians, Jamaicans, and US blacks. Am J Clin Nutr. 1998;67:391–396.
101. Santos JL, Pérez-Bravo F, Albala C, Calvillán M, Carrasco E. Plasma leptin and insulin levels in Aymara natives from Chile. Ann Hum Biol. 2000;27:271–279.
102. Bribiescas RG. Serum leptin levels and anthropometric correlates in Ache men and women of eastern Paraguay. Am J Phys Anthrop. 2001;115:297–303.
103. Hardie L, Trayhurn P, Abramovich D, Fowler P. Circulating leptin in women: A longitudinal study in the menstrual cycle and during pregnancy. Clin Endocrinol. 1997;47:101–106.
104. Messinis IE, Milingos S, Zikopoulos K, Kollios G, Seferiadis K, Lolis D. Leptin concentrations in the follicular phase of spontaneous cycles and cycles superovulated with follicle stimulating hormone. Hum Reprod. 1998;13:1152–1156.

105. Chehab FF, Lim ME, Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. Nat Genet. 1996;12:318–320.
106. Chehab FF, Mounzih K, Lu R, Lim ME. Early onset of reproductive function in normal female mice treated with leptin. Science. 1997;275:88–90.
107. Cheung CC, Thornton JE, Kuijper JL, Weigle DS, Clifton DK, Steiner RA. Leptin is a metabolic gate for the onset of puberty in the female rat. Endocrinol. 1997;138:855–858.
108. Plant TM, Durrant AR. Circulating leptin does not appear to provide a signal for triggering the initiation of puberty in the male rhesus monkey (Macaca mulatta). Endocrinol. 1997;138: 4505–4508.
109. Heger S, Partsch CJ, Peter M, Blum WF, Kiess W, Sippell WG. Serum leptin levels in patients with progressive central precocious puberty. Pediatr Res. 1999;46:71–75.
110. Witchel SF, Arslanian S, Lee PA. Leptin concentrations in precocious puberty or untimely puberty with and without GnRH analogue therapy. J Pediatr Endocrinol Metab. 1999;12:839–845.
111. Andrelli F, Hanaire-Broutin H, Laville M, Tauber JP, Riou JP, Thivolet C. Normal reproductive function in leptin-deficient patients with lipoatropic diabetes. J Clin Endocrinol Metab. 2000;5:715–719.
112. Demerath EW, Towne B, Wisemandle W, Blangero J, Chumlea WC, Siervogel RM. Serum leptin concentration, body composition, and gonadal hormones during puberty. Int J Obes Relat Metab Disord. 1999;23:678–685.
113. Kiess W, Reich A, Meyer K, Glasow A, Deutscher J, Klammt J, et al. A role for leptin in sexual maturation and puberty? Horm Res. 1999;51(Suppl 3):55–63.
114. Ong KK, Ahmed ML, Dunger DB. The role of leptin in human growth and puberty. Acta Paediatr. 1999;Suppl 88:95–98.
115. Blum WF, Englaro P, Juul A, Hertel T, Heiman M, Attanasio A, et al. Serum leptin levels in healthy children and adolescents. Horm Res. 1996;46(Suppl 2):66.
116. Mantzoros C, Flier J, Rogol A. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J Clin Endocrinol Metab. 1997;82:1066–1070.
117. van Wyk, JJ. Hormones in normal and aberrant growth. In: Williams RH (ed). Textbook of Endocrinology, 6th ed. Philadelphia: Saunders, 1981:1149–1191.
118. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med. 1994;331:1056–1061.
119. Ellison PT. Threshold hypotheses, developmental age, and menstrual function. Am J Phys Anthrop. 1981;54:337–340.
120. Ellison PT. Skeletal growth, fatness, and menarcheal age: A comparison of two hypotheses. Hum Biol. 1982;54:269–281.
121. Elizondo S. Age at menarche: Its relation to linear and ponderal growth. Ann Hum Biol. 1992;19:197–199.
122. Moerman ML. Growth of the birth canal in adolescent girls. Am J Obstet Gynecol. 1982;143:528–532.
123. Eveleth PB, Tanner JM. Worldwide Variation in Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1990.
124. Ellison PT, Lager C, Calfee J. Low profiles of salivary progesterone among college undergraduate women. J Adol Health Care. 1987;8:204–207.
125. Lipson SF, Ellison PT. Normative study of age variation in salivary progesterone profiles. J Biosoc Sci. 1992;24:233–244.
126. Ellison PT. Age and developmental effects on adult ovarian function. In: Rosetta L, Mascie-Taylor NCG (eds). Variability in Human Fertility: A Biological Anthropological Approach. Cambridge: Cambridge University Press, 1996:69–90.
127. Ellison PT. Developmental influences on adult ovarian function. Am J Hum Biol. 1996;8:725–734.
128. Apter D, Raisaen I, Ylostalo P, Vihko R. Follicular growth in relation to serum hormonal patterns in adolescent compared with adult menstrual cycles. Fertil Steril. 1987;47:82–88.

5

ENDOCRINOLOGY OF GROWTH

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INTRODUCTION

Postnatal growth can be considered to consist of at least three distinct phases: infancy, childhood, and puberty. The infancy component is largely a continuation of the longitudinal growth process observed in utero. This displays a peak growth velocity around 27–28 weeks of gestation with a decline in growth rate during the last trimester of pregnancy. Birth, in a sense, is incidental to this declining growth rate, which continues during the first 3 years of life, reaching a plateau at or around the fourth year of life and remaining at this level until the commencement of the pubertal growth spurt. This plateau is interrupted in a large number of children by a "juvenile" or "mid-growth" spurt of small magnitude, which occurs between 6 and 8 years of age. The factors influencing these distinct growth periods are different. We know little of the factors influencing fetal and early infant growth but know from animal experiments that nutrition plays a key role. With the appearance of the growth hormone (GH) receptor in the growth plate at around 6 months of postnatal life, the GH-dependent growth assumes greater importance and during the childhood years, growth is largely dependent on the GH secretory status of the individual. The final step in the growth process, the pubertal growth spurt, comprises a 50% contribution from sex steroids and 50% contribution from GH.

This chapter initially outlines our understanding of factors involved in regulating fetal growth with particular emphasis on the insulin-like growth factor (IGF) axis. This allows us to compare and contrast the role of the IGF axis in the regulation of fetal and postnatal growth. In the understanding of the endocrinology of growth, it is important to realize that, during postnatal growth, a large number of factors influence the growth process, but the majority of these operate through modulation of the GH axis. This is not to say that all growth failure in childhood is due to GH deficiency but rather that GH acts as a final common pathway for the integration of all these signals. For example, patients with celiac disease grow poorly due to malabsorption, but in addition their GH response to a number of provocative stimuli is blunted. They are not, per se, GH insufficient, as the GH secretion returns to normal once the underlying abnormality in the gastrointestinal tract is rectified.

Any consideration of the growth process, particularly in the postnatal period, requires an understanding of the physiology of GH secretion. GH secretion takes place in a pulsatile manner and it is important to understand the part played by this pattern in the generation of growth in the human.

ENDOCRINOLOGY OF GROWTH

GH Secretion—Cellular and Molecular

The pituitary gland develops as an outpouching of the stomatodeum—Rathke's pouch. The process takes place between 30 and 35 days postconception and is tightly regulated by a series of homeobox genes. Close apposition between this structure, which is destined to form the anterior pituitary, and the base of the hypothalamus takes place; and this leads to descent of neural tissue with the pouch to form the posterior pituitary. Stalk vascular cannulization completes the process. Differentiation of the anterior pituitary mass into the recognizable cell types is influenced in part by the homeobox genes involved in development and cell-specific homeobox gene expression. Somatotroph cell differentiation utilizes in addition the expression of two genes: Prop-1 and Pit-1. Enlargement of the somatotroph cell number requires the induction of the growth hormone releasing hormone (GHRH) receptor by Pit-1. This allows the hypothalamic peptide to stimulate somatotroph cells, leading to synthesis and release of GH. In addition, GHRH stimulation also leads to somatotrophic hyperplasia.

The human GH gene is located on chromosome 17, along with two genes for human somatomammotropin (Figure 5-1). Pituitary GH is coded for by the hGHN gene and transcription leads to the synthesis of GH with a molecular weight of 22 KD. The excision of the second intron of hGHN leads to an alternative splicing site, resulting in deletion of the message for amino acid residues 32-46, the 20 KD GH variant. This forms 10% of the circulating GH.

The synthesis of GH is regulated largely by the levels of GHRH impinging on the anterior pituitary somatotropes. GHRH acts on the somatotrope by binding to its own specific receptor, which activates a secondary messenger system via cyclic AMP synthesis. This receptor is characterized by seven transmembrane loops and internal coupling to the G(guanine)-protein system (Figure 5-2). In their resting state, the G-proteins exist as heterodimeric complexes with α, β, and γ subunits. In practice, the β and γ subunits associate with such a high affinity that the functional

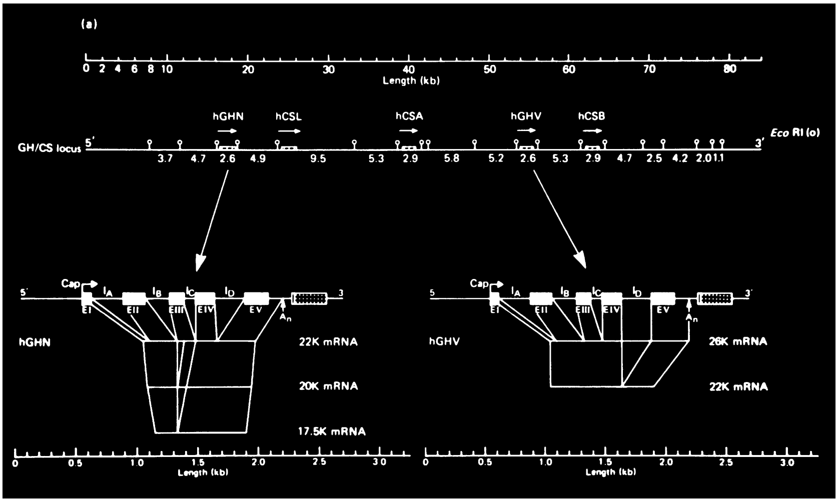
(a)
0 2 4 6 8 10 20 30 40 50 60 70 80
Length (kb)
hGHN
hCSL
hCSA
hGHV
hCSB
GH/CS locus
5'
3'
Eco RI (a)
3.7 4.7 2.6 4.9 9.5 5.3 2.9 5.8 5.2 2.6 5.3 2.9 4.7 2.5 4.2 2.0 1.1
Cap
IA IB IC ID
EI EII EIII EIV EV
An
hGHN
22K mRNA
20K mRNA
17.5K mRNA
hGHV
26K mRNA
22K mRNA
0 0.5 1.0 1.5 2.0 2.5 3.0
Length (kb)

FIGURE 5-1 The human GH gene cluster with enlargement of the DNA coding for hGHN (pituitary) GH and hGHV (placental) GH.

units are G_α and $G_{\beta\gamma}$. After association of the G-protein complex with the occupied receptor, conformational changes in the α subunit lead to an increased rate of dissociation of GDP, which is replaced by GTP. This guanine nucleotide exchange in turn causes the α subunit to dissociate from the heterotrimeric complex. The liberated α subunit, together with its activating GTP, then binds to a downstream catalytic unit adenylate cyclase.

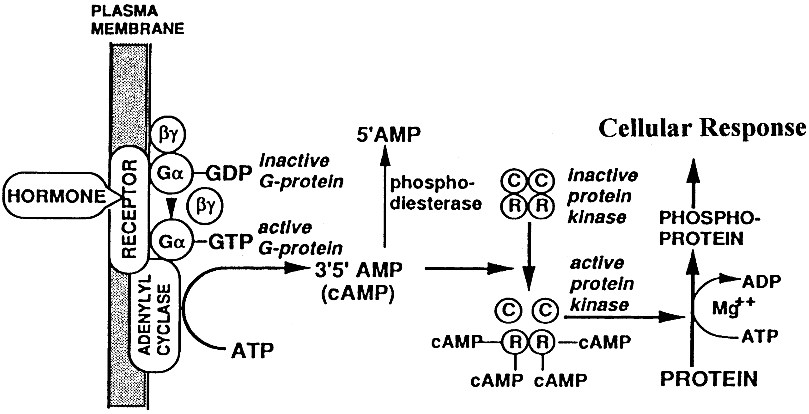
PLASMA MEMBRANE
HORMONE
RECEPTOR
βγ
Gα
GDP
Inactive G-protein
βγ
Gα
GTP
active G-protein
ADENYLYL CYCLASE
ATP
3'5' AMP (cAMP)
5'AMP
phospho-diesterase
C C
R R
inactive protein kinase
active protein kinase
C C
cAMP R R cAMP
cAMP cAMP
Cellular Response
PHOSPHO-PROTEIN
ADP
Mg++
ATP
PROTEIN

FIGURE 5-2 Schematic representation of G protein system with activation of cyclic AMP (cAMP) or calcium (Ca^{2+}) or diacylglycerol (DAG).

Hydrolysis of the GTP bound to G_α due to its intrinsic GTPase activity liberates the G_α subunit from the catalytic subunit and allows reassociation of G_α GDP with the $G_{\beta\gamma}$. This newly reformed heterotrimer then returns to the G-protein pool in the membrane. In this way, an individual G-protein complex is recycled, so that it can respond to further receptor occupation by ligand.

$G_{s\alpha}$ activates membrane bound adenylyl cyclase, which catalyses the conversion of ATP to the potent second messenger cAMP. This cyclic nucleotide in turn activates a cAMP-dependent protein kinase (PKA), which modulates multiple aspects of cell function. PKA phosphorylates a transcription factor called CREB (cAMP response element binding protein). This is then translocated to the nucleus, where it binds to a short palindromic sequence in the promoter region of the GH genes, the process that leads to transcription and synthesis of GH. The transcription of the GH gene is regulated in turn by a number of other hormones such as thyroxine and cortisol.

Physiology of GH Secretion

Prior to consideration of the endocrine regulation of different stages of human growth, it is worth considering the physiology of the GH-insulin-like growth factor axis. Figure 5-3 shows this particular pathway as a classic closed loop feedback system. Figure 5-4 shows a typical GH profile in a 9-year-old boy generated by taking blood samples for GH measurement every 20 minutes.

Frequent sampling is essential to define clearly the true heights of the peaks. If sampling were too infrequent, the true peak heights might be underestimated or peaks missed altogether. The profile is characterized by episodes of GH release, generating peak GH concentrations, interspersed with periods when GH secretion is effectively switched off and GH concentrations are undetectable. This appears to be the predominant pattern in males, whereas in females in varying species, although the peak concentrations tend to be similar, the most striking difference is that there is an elevation in the trough concentrations, so that at all times concentrations are detectable. One further point to note is that the pulses occur at fairly frequent intervals of one every 3 hours, suggesting that most of the GH signal is contained in the amplitude of the pulses.

In both rodents and humans, evidence supports the concept of an inverse relationship between the secretion of the two hypothalamic peptides: somatostatin (SS) and GH releasing hormone. GHRH is involved in both the release and synthesis of GH while SS inhibits GH release. Normal GH pulsatility requires endogenous GHRH, although GH responses to exogenous GHRH are variable and reveal varying periods of responsiveness and refractoriness. There are several possible explanations for this. First, the phenomenon may be intrinsic to the GH-secreting cells. Second, acute downregulation of the GHRH receptors or their intracellular signaling systems may take place. This appears to be an unlikely explanation as downregulation takes place only at very high GHRH levels, certainly well above those usually encountered physiologically. Third, it could be by depletion of the read-

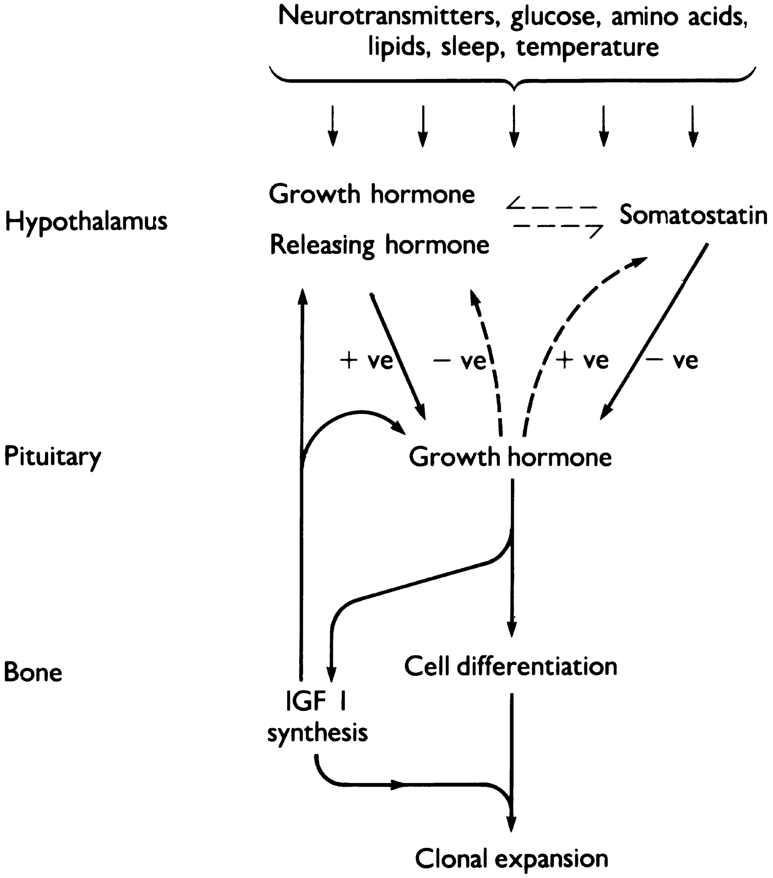
Neurotransmitters, glucose, amino acids, lipids, sleep, temperature
Hypothalamus
Growth hormone Releasing hormone
Somatostatin
+ ve
− ve
+ ve
− ve
Pituitary
Growth hormone
Bone
Cell differentiation
IGF I synthesis
Clonal expansion

FIGURE 5-3 Growth hormone cascade.

ily releasable pool of GH. The final and most likely explanation is that the pattern reflects variation in endogenous SS tone imposing an ultradian rhythm in GHRH responses. Evidence for this comes from the observation that continuous GHRH administration leads to pulsatile GH release, implying modulation by another factor, somatostatin. Although SS readily suppresses pulsatile GH secretion in rats and humans, its effects are short-lived and rapid release of GH takes place on SS removal. This rebound secretion can be detected in vitro but is even more pronounced in vivo. In general, GHRH administration alone leads to the gradual attenuation of the GH response with time. SS withdrawal can produce GH rebound secretion in the human subject, but for regular repeatable GH release to take place, the combination of SS withdrawal coupled with GHRH administration is the most efficacious.

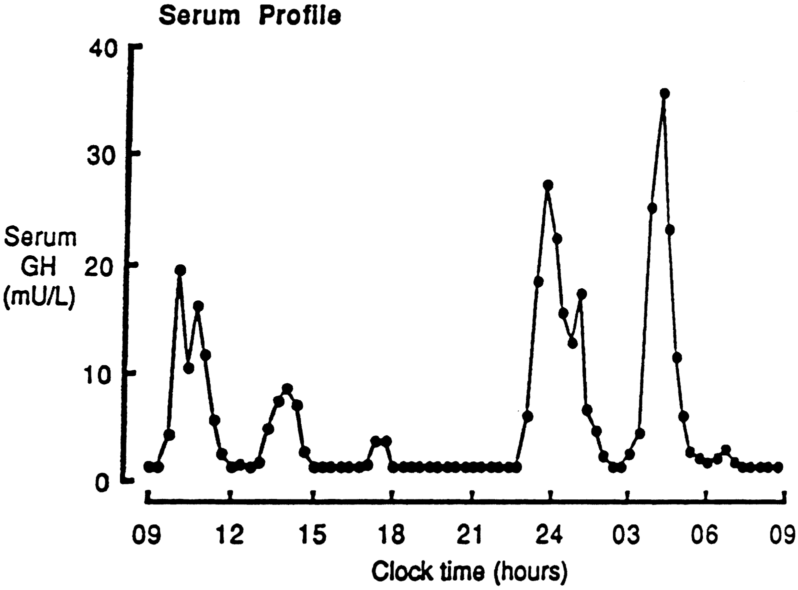

FIGURE 5-4 Twenty-four-hour serum GH concentration profile.

The close relationship between GHRH and SS acting as integrators of other signals, such as sleep, is complicated by the recent discovery of a family of GH secretagogues, which differ substantially from GHRH in both their structure and receptors. These GH secretagogues behave in a similar manner in terms of their physiology as GHRH, but the important difference is that they act synergistically with GHRH to generate GH release (Figure 5-3). Recent work has identified the endogenous "third factor" as Ghrelin, which is present in the stomach. The precise physiology of this substance remains to be determined. A number of endogenous agents affect GH pulsatility, including opioids, calcitonin, and glucagon, but these have not been used to manipulate GH secretory patterns to alter growth and their physiological relevance to the control of endogenous pulsatility remains unclear.

There is good evidence that GH feeds back to inhibit its own release, and this may have a bearing on the temporal control of GH pulsatility. Experiments indicate that exogenous GH acts directly on the hypothalamus rather than on the pituitary. The most likely mode of action of GH is through increased secretion of SS into the portal blood, but there is evidence that GH also leads to an inhibition of GHRH production. In addition, GH can also feed back indirectly by the generation of IGF-1, which in turn inhibits GH synthesis and release chiefly at the pituitary level.

The secretion of GH into the circulation is pulsatile. The entry rate of endogenous GH is governed by the kinetics of GH release from the somatotropes and the removal from the circulation is largely determined by the amount of GH bound to its binding protein and internalized by the GH receptor on the target organ cells. The precise role of the binding proteins in humans, at least, is far from clear. There is correlation with GH status but only at the very extremes, and the effect of GH treatment is highly variable. Although GH binding protein might increase the amount of GH available for constant delivery of GH to the receptor, this is not at all clear. There is no evidence to suggest that the preferred mode of presentation of GH to the receptor is continuous. A body of evidence suggests that the pulsatile mode is most optimal. An alternative role for the binding proteins might be to buffer the system from overexposure to GH. Given the high affinity of GH for its binding protein this might be a more likely explanation.

The pulsatile signal appears to be important in determining a number of target organ effects. For example, in rodents, the pattern of hormone secretion, either pulsatile (male mode) or continuous (female mode), has an impact on the growth of the animal, expression of a number of liver enzymes, the determination of the level of GH binding protein in the circulation, as well as GH receptor expression. The tissue response is also variable in that the liver generates IGF-1 in response to GH irrespective of the mode of administration, whereas adequate expression of IGF-1 in the muscle is highly dependent on the pulsatile mode of administration.

Increasing evidence in humans suggests that the mode of GH secretion is important in determining target organ response. In humans, IGF-1 generation occurs best when GH is present in the pulsatile rather than the continuous mode at least in the physiological situation. This may not be the case when GH treatment uses the subcutaneous route, as the pharmacokinetics of subcutaneous GH tend toward a more continuous exposure. On the other hand, the pattern of fat distribution around the abdomen is influenced more by the trough concentrations of GH in humans.

GH Receptor and Target Organ Signaling

The GH receptor together with those for the cytokines, such as the interleukins and erythropoietin, share a common major structural feature in that they have four long alpha-helixes arranged in an antiparallel fashion. As a consequence, this subgroup is commonly referred to as the cytokine/hemopoietic receptors. The structure of human GH with its receptor is a ternary complex consisting of a single molecule of the hormone and two receptors. After GH has bound to one molecule of receptor, this is followed by association of this complex with a second receptor molecule. The dimerization of the cytoplasmic region in the ternary complex is particularly important for signal transduction.

The GH receptor uses an unusual intracellular signaling system: Janus-associated kinase-2 (JAK-2). The JAK system is coupled to further intracellular proteins, the so-called STAT proteins (Figure 5-5). These are transcription factor proteins. They contain a crucial tyrosine residue located in the carboxy-terminal in a homologous position in all STAT proteins (residue 694), and phosphorylation of this is essential for STAT activation. STAT proteins have dual functions: signal transduction in the cytoplasm followed by activation of transcription in the nucleus. The family members of STAT proteins have been named in the order of their identification. GH induces tyrosine phosphorylation of STAT proteins 1, 3, 5a, and 5b, but STAT 5 is probably the major axis of the JAK-STAT cascade. Dimerization of the STAT proteins appears to be essential for their final translocation to the nucleus, where they activate immediate early response genes that regulate proliferation or more specific genes that determine the differentiation status of the target cell.

GH AND IGF-1 AXIS AND ITS ASSOCIATION WITH FETAL GROWTH

Given the paradigm depicted in Figure 5-1, it is interesting to contrast the situation in the fetus with that in the child and the adolescent. The fetus is subject, particularly in the latter half of pregnancy, to a fairly constant delivery of metabolites via the placenta. The flow of metabolites continues through the umbilical vein, and the distribution thereafter utilizes a circulatory pattern in which blood is predominantly diverted in its oxygenated form to the developing brain. Given that the fetus is highly dependent on this mode of delivery of substrate, perhaps it is not too surprising that the growth process differs. In addition, the growth of the individual organs also differs from that observed in postnatal life with different patterns of growth and development exhibited by many of the differing tissues.

Studies in larger domestic animals show that pulsatile secretion of GH and other pituitary hormones is already demonstrable in fetal life and is sensitive to nutrition. Little is known about the evolution of GH secretion in the human fetus. Stud-

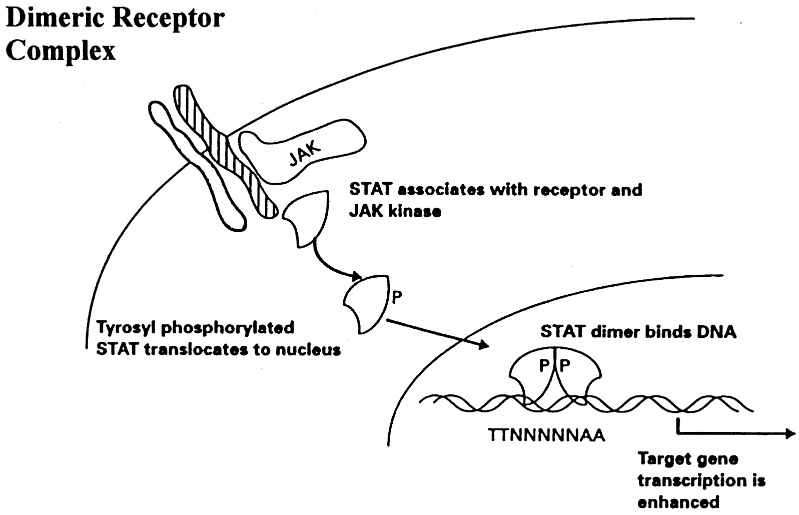
Dimeric Receptor Complex
JAK
STAT associates with receptor and JAK kinase
P
Tyrosyl phosphorylated STAT translocates to nucleus
STAT dimer binds DNA
P P
TTNNNNNAA
Target gene transcription is enhanced

FIGURE 5-5 Dimeric receptor (GH and receptor) signaling through JAK kinases.

ies have demonstrated a gradual increase in circulating GH concentration during the first 12 weeks of pregnancy, reaching a peak at 20–24 weeks and declining toward birth. These early changes to serum GH concentrations appear to parallel the known development of the hypothalamic peptides GHRH and SS. The human fetal pituitary is able to respond to these two factors, and it is proposed that the GHRH effect predominates, with SS increasing in effect toward term. Even at term, GH levels are 20–30 times higher than those observed in childhood, but perhaps of greater importance is that the levels are continuously elevated and lack the pulsatile pattern observed in childhood and adult life. However, these high GH concentrations are not associated with elevated levels of IGF-1 in the fetus, implying that there is "relative resistance" to the effects of GH in the fetus. The effect may diminish toward term but it can be assumed that GH is not the predominant determinant of fetal growth. This is also borne out by experiments of nature in which the GH gene is deleted or where the GH receptor is nonfunctional. These individuals are normal size at birth when due account is taken of maternal size.

Because of the problems associated with accessibility to human fetal tissue, the role of endocrine factors in determining fetal growth is largely inferred from studies in animals. The most elegant series of these studies involves the use of transgenic animals in which the various components of the IGF axis (Table 5-1) have been knocked out. It must be appreciated that these studies reveal quite major effects of the whole gene and tell us that the peptide is of particular importance in the determination of size of the fetus. That they clearly are important comes from the observation that many of the knockout offspring die in the first few hours of life. Table 5-1 shows the type of knockouts that have been constructed, and from this, both IGF-1 and IGF-2 can be clearly seen to play important roles in the determination of body size in the mouse. It is likely that a similar situation pertains in the human, because there is a clear relationship between birth weight and levels of both these growth peptides; in addition, a boy with IGF-1 gene defect was born with low birth weight. Perhaps rather surprisingly, loss of the insulin gene did not appear to alter body size. This would, at first sight, appear contradictory to clinical observations of macrosomia associated with maternal hyperglycemia and the condition of hyperinsulinemic hypoglycemia of infancy, where excess fetal and neonatal insulin production leads to fetal overgrowth. It is likely that in these situations the effects of hyperinsulinemia in the fetus are mediated via the IGF receptors rather than a direct effect of insulin via its own receptor. The IGF receptor knockout studies indicate the importance of the Type 1 IGF receptor in mediating the growth effects of IGF-1 and IGF-2. All these studies demonstrate a pivotal role for the IGF family in the determination of fetal growth.

In the newborn, studies have revealed markedly amplified GH secretory episodes that occur throughout the day and night. Preterm infants have even higher secretory profiles than term babies. The high GH secretion at birth is sensitive to inhibition by dopamine and by stimulation by intravenous GHRH. The GH response to GHRH is in turn modified by the birth size of the baby, with greater responses seen in those of lower birth weight. As IGF-1 levels are lower in these babies, this

TABLE 5-1 Results of IGF and Insulin Knockout Mice Studies

Inactivation	Fetal Size
IGF-1/IGF-2	30%
Insulin receptor	100%
Type 1 IGF receptor	45%
+IGF-1	Fatal
+IGF-2	30%

might imply that the feedback effect of IGF-1 is also operative at this age. However, as IGF-1 levels are generally lower at birth and increase thereafter through childhood into adolescence, it is possible that elevated GH values may represent, in part, "immaturity" in this part of the feedback loop. Although the GH response to SS is blunted, the components for generating episodic secretion are clearly present and become more operative during the neonatal period.

ENDOCRINOLOGY OF PREPUBERTAL GROWTH

After 2–3 months of life, clinical evidence suggests that GH is necessary for sustaining normal growth. The postnatal elevated GH levels observed subside, so that by 3–6 months of age, values approach those observed in childhood. During the prepubertal years, GH secretion gradually increases, primarily in terms of the amplitude of the GH pulses.

Although many reports demonstrate differences in GH secretion between tall normal and short stature children and between those with normal stature and short stature, the differences pertain more to the growth rates of the individuals than the stature observed (Figure 5-6). These differences in GH secretion are reflected in the serum levels of IGF-1 seen in these groups. IGF-1 values increase gradually from birth throughout childhood and relate well to the levels of GH secreted. Apart from pathological conditions, it remains difficult to relate any measure of GH pulsatility to the observed growth rate in individual children with short stature, probably because the variability in growth rate is so small.

The situation is complicated further by the interaction of body composition with GH secretion. Particularly in the area of short stature that is a heterogeneous condition, we can imagine a number of diagnoses impinging on the growth process that also influence the relationship between growth and GH. Generally speaking, height at its extremes can be related to GH secretory status. In situations where body mass index is controlled for, the more important relationship is that between GH secretion and growth rate. The relationship has been documented by several groups and is probably described as a curvilinear relationship (Figure 5-7).

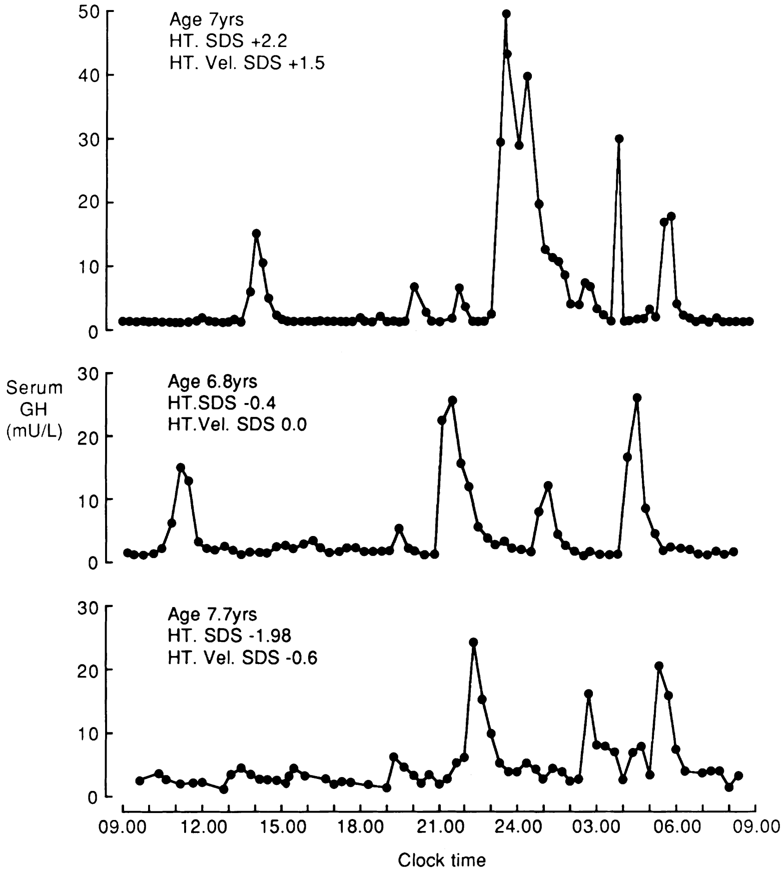

FIGURE 5-6 Effects of age, stature, and growth rate on 24-hour serum GH profiles.

These observations tend to relate to long-term growth, over a period of 1 year usually, with GH secretion on a particular day. More detailed studies using repeated estimations of GH secretion in urine have linked GH secretion not only to growth rate but also to the intraindividual variation in growth rate that occurs on a week-by-week basis.

Considerable interest has centered on the components of the GH profile that contribute to the effect on growth. Early studies demonstrated that the growth process was pulse amplitude modulated and that GH pulse frequency did not change, remaining relatively fixed at a 200-minute periodicity. Changes in pulse frequency are largely confined to pathophysiological states, such as poorly controlled diabetes mellitus. Paradoxically, poor growth in chronic renal failure is associated with high GH secretion or at least high GH levels in the circulation, which in part

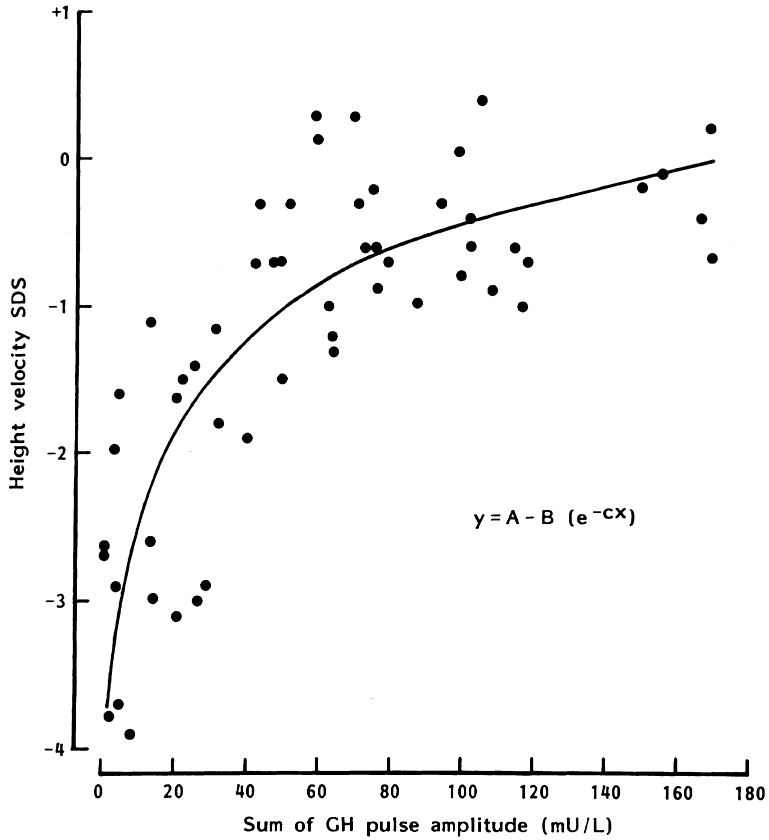

FIGURE 5-7 Asymptotic relation between height velocity expressed as a standard deviation score (SDS) and the sum of GH pulses secreted over a 24-hour period.

may result from reduced GH clearance, although a degree of GH hypersecretion probably exists as well.

The pulse amplitude is determined predominately by the rate of entry of GH to the circulation. As the duration of the pulse is relatively fixed, the rate of change of GH in the circulation then becomes an important factor. Several studies suggested that the rate of rise of the pulse is the actual growth signal, so that the main information is actually contained in the rate of change of hormone concentration rather than in the actual level achieved. This rather presupposes that there is an actual level above which growth is likely to take place and that any further modulation is due to the rate of rise of the hormone secreted. This has not been tested formally but remains an intriguing possibility. The suggestion is not too far-fetched and it appears to be borne out to a certain extent by receptor studies. Rapid receptor turnover would be a prerequisite in pulsatile systems, and this is certainly the case with the insulin receptor in fat and muscle. Fairly rapid internalization takes place with the GH receptor, and the intracellular signaling system functions optimally with a 3-hour change in ambient GH concentrations.

One further component of the profile that appears to be important: the trough concentration of GH achieved in a secretory profile. Mention has already been made of the importance of the secretory pattern in rodents and to an extent in humans on influencing the generation of IGF-1 and for the maintenance of body composition. The precise role of trough concentrations in altering, or rather influencing, growth rate in humans is still far from clear. However, evidence suggests that, although the predominant effect on growth is determined by the amplitude of the GH secretory pulses, the effect of this pulse is modulated to a certain extent by the level of trough concentration. In the situation where the GH pulse amplitude is sufficient to generate normal growth, alterations in trough concentration appear to affect but little the overall growth rate. In the situation where GH secretion is attenuated due to a low GH pulse amplitude with consequent reduction in growth rate, the presence or absence of trough levels of GH has a profound effect on the growth rate observed. A situation of low GH pulse amplitude combined with a high trough concentration is associated with an extremely poor growth rate, compared to that observed with a similar GH pulse amplitude and a lower or normal trough concentration. These effects on growth rate are mirrored in the levels of serum IGF-1 concentration measured (Table 5-2).

Surprisingly little is known about the effect of alterations in GH receptor status and its effects on growth in normal individuals. Apart from the situation of GH receptor deficiency due to genetic abnormalities in the GH receptor gene, little is understood about differences in sensitivity to GH between individuals. This is a rather surprising situation, given that GH has been used for the treatment of a number of growth disorders over many years. The syndrome of GH resistance due to abnormalities in the GH receptor leads to an individual who produces considerable quantities of GH but very small amounts of IGF-1 or the other GH independent protein, IGF binding protein 3. The net result is a growth phenotype similar to but

TABLE 5-2 Growth Rate and IGF-1 Levels in 50 Children with Respect to Peak and Trough GH Concentrations (data shown as mean value)

	GH Peak <50th	GH Peak >50th	Total
Height Velocity Standard Deviation Score			
GH Trough <50th	–1.38	–0.82	–1.05
GH Trough >50th	–1.93	–0.72	–1.37
Total	–1.70	–0.77	
Serum IGF-1 Concentrations (U/1)			
GH Trough <50th	0.44	0.53	0.49
GH Trough >50th	0.21	0.43	0.31
Total	0.31	0.49	

probably more severe than individuals with GH gene deletion. The treatment of these individuals with IGF-1 is only partially successful, probably because GH is also required in its own right in the commitment of stem cells to the proliferative and hypertrophic zones of the cartilage. What happens during IGF-1 treatment is that any endogenous GH is suppressed, hence any chance of stem cells entering the proliferative zone is reduced and the effect of IGF-1 is simply to proliferate those cells available and gradually reducing in number during the course of therapy.

A few studies have suggested difference in GH sensitivity in the general population, but the lack of good dose response curves to adequately define the terms has seriously hampered the development of concepts in this area.

As suggested, the GH axis acts as a final common pathway in childhood for a number of pathophysiological situations affecting growth. In acquired hypothyroidism, there is a general permissive effect of thyroid hormone on the whole growth axis. In hypothyroidism, there is a reduction of the efficacy of GHRH-stimulated GH release, probably as a result of a reduction in the transcription of the GH gene. Any GH secreted has probably less of an effect on the target tissues, as quite good evidence suggests that thyroxine is particularly important for mediating GH action at target tissue level. This is in addition to the effect of post-GH receptor of thyroxine on cartilage growth.

Although GH plays an important role in prepubertal growth, there is probably an interaction with other factors. The juvenile or mid-growth spurt is a good example of this. If an individual's growth chart is examined, an increase in growth rate can be detected around 6–8 years old. The precise etiology of the spurt is unclear, but it is likely that adrenal androgens, which are increasing in circulatory concentration at this time, play a role. Supportive evidence comes from patients with early onset Addison's disease, where adrenal function is lost. Patients with this disease do not manifest a mid-childhood growth spurt, or at least it is attenuated. Of interest is the observation that these patients and indeed anyone who has suppressed adrenal androgen secretion have delay in the timing of the onset of puberty. This suggests that adrenal androgen production is involved not only in the mid-childhood growth spurt but also in priming the hypothalamopituitary axis for puberty.

ENDOCRINOLOGY OF PUBERTY

The pubertal growth spurt in human subjects represents the contribution of sex steroids and GH each contributing 50% of the height gained. Augmentation of GH secretion occurs during puberty with an approximate two- to threefold increase in amplitude of the secretory bursts, whereas the frequency of GH pulses does not change. Many cross-sectional studies demonstrated that the increase in GH pulse amplitude coincides with the pubertal growth spurt and confirmation of this observation has come from detailed longitudinal studies where puberty has been induced with the hypothalamic peptide gonadotropin-releasing hormone (Figure 5-8).

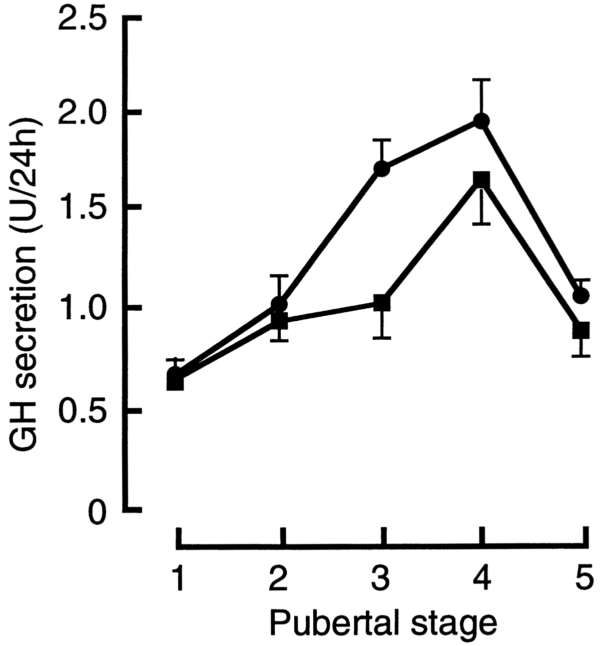

FIGURE 5-8 Changes in GH production during a 24-hour period in females (closed circles) and males (closed squares) at different stages of pubertal development.

Sex steroids play an important role in regulating the physiology of GH secretion in childhood. Estrogen has long been known to alter GH responses to stimuli and small doses of estrogen, when given to girls with gonadal dysgenesis, enhance GH secretion, as does testosterone administration to boys with delayed puberty. Conversely, suppressing puberty, as in the situation of precocious puberty, with a gonadotropin-releasing hormone analogue leads to a decrease in GH secretion. Both testosterone and estradiol stimulate GH, so the question arises as to whether they act as independent agents. Nonaromatizable androgens such as oxandrolone do not greatly effect GH secretion. The effect of testosterone is certainly time and probably dose dependent. Androgen receptor blockade has little effect on GH secretion, while the antiestrogen tamoxifen blocks testosterone stimulation of GH secretion, suggesting that aromatization of testosterone to estradiol, which then acts via the estrogen receptor, may be more important for testosterone effects on GH.

The precise mechanisms by which the sex steroids alter the interaction of GHRH and SS in the generation of GH pulses in childhood is unclear. However, a large amount of experimental data, primarily from the rat, suggests that neonatal exposure to steroids has an imprinting effect on the hypothalamic systems regulating

GHRH and SS, but their full expression of this requires continued gonadal steroid exposure in adult life. Prepubertal gonadectomy can markedly alter the expression of the sexually dimorphic GH secretory pattern in the adult rat. In addition to the hypothalamic effects, the raised basal GH release by estradiol in normal rats may be due to effects directly on pituitary GH synthesis or GH cell number.

Estrogen has additional effects on the growth process. The dose-response effect between estrogen and growth is biphasic in nature, with a peak acceleration in growth observed with ethinyl estradiol doses of approximately 10 μg per day, which is equivalent to the midpoint of pubertal development. Increasing the estrogen dose leads to a reduction in growth rate and an advance in skeletal maturation. It would appear that estrogen has two effects in puberty. The first is to augment GH secretion in lower doses, leading to generation of the pubertal growth spurt and, at higher doses, certainly in the rat, to suppression or at least reduction in GH release; the second is to accelerate ossification and closure of the growth plate. This latter process appears to depend highly on the density of estrogen receptors in the growth plate. In experiments of nature where estrogen is either deficient due to aromatization defects or unable to act due to estrogen receptor mutation, growth continues, albeit slowly, and the epiphyses do not close.

GH SECRETORY PATTERNS IN ADULTHOOD

Serum GH concentrations and pulsatile GH secretion fall in early adulthood by 25 or 50% of the values observed during puberty. This is a particularly interesting observation in view of the fact that the concentrations of sex steroids, which are associated with the increase in GH secretion, have changed but little during the latter part of puberty. As suggested already, the overall suppressing effect might arise as a result of the biphasic action of estrogen on GH secretion, but evidence to support this suggestion is lacking in the literature. The aging process itself may well have an important effect on the number and size of the somatotropes in the pituitary and also on GH gene expression, both decreasing with age. Clinical studies with GHRH-stimulated GH release support the concept of a decreasing GH releasable pool with age, as do exercise studies.

It is probably also worth mentioning the studies conducted in adulthood, which probably pertain to the endocrinology of growth in childhood. Gender, body composition, and exercise play important roles in determining circulating GH concentrations. The sexual dimorphic patterns of GH secretion in humans are discussed earlier in this chapter. The gender effect is certainly less marked than in the rodent but clear differences between males and females can be demonstrated. Gender is also a strong modifier of the negative impact of age. The major change of GH secretion with age is the diminution in GH pulse amplitude, and the presence of sex steroids would seem to be important, since women at premenopausal age with normal levels of estrogen are relatively protected from the negative effects of increasing age. This effect is not seen in the postmenopausal age group. There is, in addition, a further interaction between gender and the effects of both adiposity and GH secretion.

CONCLUSION

The human growth process can be broken down into at least three distinct phases of growth: infancy, childhood, and puberty. Further subdivisions probably could be made, but at least these three phases are regulated by different aspects of the endocrine system. Very little is known about antenatal growth and growth in the first year of life. The information available, however, strongly suggests that growth in utero and probably in the first 6 months of life is largely GH independent. The precise factor(s) that determine this growth process are still unclear. The nutritional status of the individual is clearly an important determinant, but the precise factors that translate nutrient input into growth remain to be defined. Transgenic technology coupled with knockout studies strongly suggest that the IGF axis plays an important role in this process. During the first year of life, there is a gradual switch from this nutritionally dependent growth process to GH dependency. Full dependence on GH for the growth process appears to be attained toward the second year of life, and thereafter the majority of childhood growth can be explained in terms of the amount of GH secreted by the individual. GH appears to be the final common pathway for integrating the effects of a number of growth signals, and in pathophysiological situations where growth is affected, abnormality in the GH axis can be expected. The pubertal growth spurt is made up by a contribution of sex steroids coupled with GH. The most important component appears to be estrogen in females and the aromatization of testosterone to estrogen in males.

SUGGESTED READING

Brook CGD (ed). Clinical Paediatric Endocrinology, 3rd ed. Oxford: Blackwell Scientific Publications, 1995.

Robinson ICAF, Hindmarsh PC. The growth hormone secretory pattern and statural growth In: Kostyo JL (ed). Handbook of Physiology, Section 7. The Endocrine System. Vol. 5. Hormonal Control of Growth. New York: Oxford University Press, 1999:329–395.

Ulijaszek SJ, Johnston FE, Preece MA. The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998:182–184.

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THE GENETIC EPIDEMIOLOGY OF GROWTH AND DEVELOPMENT

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INTRODUCTION

In spite of the predominant role of genetic variation in causing the observed variability among children in their growth and development, studies of genetic influences on growth and development are few in comparison to the plethora of descriptive studies, population comparisons, and studies of the impact of specific environmental factors. There are two main reasons for this. First, the courses of study that many investigators of growth and development are trained under (e.g., physical anthropology or human biology) usually provide little formal training in human genetics and statistical genetic analysis. And second, to study genetic influences on growth and development, data from related children are needed. Preferably those data are longitudinal, and ideally they are longitudinal data from large numbers of related children reared under different household environments. Unfortunately, such data are very rare.

The purpose of this chapter is to provide an overview of the genetic epidemiology of normal human growth and development. Although a treatise on quantitative genetic approaches to the study of growth and development is beyond the scope of the chapter, as is a complete review of the existing literature on the genetics of growth and development, the references and suggested readings provide a good starting point for the interested student to pursue further study. This chapter is meant to serve as an introduction to how auxologists can most profitably approach the study of the genetics of growth and development today.

Almost half a century ago Neel and Schull[1] proposed that the epidemiological approach can be extended to the study of nondiseased states and argued that, "genetic concepts must be an integral part of the armamentarium of the modern epidemiologist" (p. 302). The "epidemiological genetics" that Neel and Schull envisioned has become known as *genetic epidemiology*. On the establishment of the International Genetic Epidemiology Society (IGES) in 1992, its founding president, James V. Neel, succinctly defined genetic epidemiology as, "The study of genetic components in complex biological phenomena" (IGES website, http://hydra.usc.edu/IGES). From this perspective, the genetic epidemiology of growth and development may be considered as the study of the genetic underpinnings of the size, conformation, and maturity status of individuals over the course of childhood. This includes characterizing the magnitude of genetic influences on growth and development phenotypes, examining how those genetic influences operate over time, identifying and localizing specific genetic polymorphisms that contribute to variation in growth and development, and elucidating how genetic and environmental factors interact during growth and development. The advances made over the last two decades in both molecular and statistical genetics make possible the sophisticated analyses needed to elucidate the roles of genes and environment in the complex biological phenomena that constitute growth and development.

This chapter is divided as follows. We begin with an introduction to basic statistical genetic terminology. Next, different study designs used to examine genetic influences on quantitative traits are discussed. Then, we summarize published findings from various studies of the genetics of growth and development. After that, we present findings from current genetic epidemiological studies of the growth and development of U.S. children in the Fels Longitudinal Study and Nepali children in the newly established Jiri Growth Study. Throughout the chapter, important terms or concepts are in boldface the first time they are mentioned. Brief definitions of these terms and concepts can be found in the Glossary.

STATISTICAL GENETIC TERMS AND CONCEPTS

Statistical genetics refers to a variety of methods for analyzing **phenotypic** variation among related individuals. These methods include those tailored for the study of both discrete and continuous traits. Most growth and development phenotypes exhibit a continuous distribution over a delimited range, and because the growth and development status of a child can usually be measured in some way, most growth and development phenotypes are quantitative traits. Growth and development phenotypes also are referred to as being complex traits, meaning that genes at a few and perhaps several loci contribute to the variation observed in the trait, as do environmental factors, possibly through interaction with those genes. The field of quantitative genetics deals with the analysis of complex traits. As with any specialized field of study, it contains a number of specific terms and concepts. This section provides a brief discussion of those quantitative genetic terms and the concepts most important for an understanding of the genetic epidemiology of normal growth and development. Thorough discussion of quantitative genetic methods can be found in books listed in the Suggested Reading section.

Relatedness of Individuals

To start with, because related individuals are not independent but share some of their genes by virtue of a common ancestry, it is necessary to consider their degree of relatedness in assessing their degree of resemblance for a trait. The **kinship coefficient** between two individuals is the probability that an **allele** taken at random from the two alleles at a **locus** in one individual is identical to an allele taken at random from the two alleles at the same locus in another individual. The kinship coefficient between first degree relatives is 0.25, meaning that, for example, between a pair of full siblings there is a 25% chance that at a locus each has the very same allele that they each inherited from a common ancestor.

Most of what we know about the genetic control of growth and development comes from family-based studies, in which the correlations between relatives and between unrelated individuals for a trait such as stature or weight are calculated. The basic premise underlying these investigations is straightforward: If the variation in a trait is largely under genetic control, then related individuals will be more similar for the trait than unrelated individuals (i.e., the intrafamily variance of the trait is low compared to the interfamily variance). Conversely, if the variation in a trait is only partly determined by genes, then related individuals may resemble each other only a little bit more than unrelated individuals (i.e., the intrafamily variance of the trait is a little smaller than the interfamily variance).

Heritability

Through examination of correlations between different pairs of relatives, heritabilities can be calculated. The concept of **heritability** (h^2) is central to understanding the nature of genetic control for any trait. The heritability of a trait is a measure of the degree of genetic control of a phenotype, ranging from 0% (no genetic effects) to 100% (complete genetic effects). Heritabilities are population level estimates, specific to a particular population in a given environment, and this can sometimes be an important consideration when comparing h^2 estimates across populations.

According to classical quantitative genetics theory (e.g., Falconer and Mackay,[2] Lynch and Walsh[3]) the observed phenotypic variation (σ_P^2) in a trait can be expressed as the sum of both genetic (σ_G^2) and random environmental effects (σ_E^2). This is written as

$$\sigma_P^2 = \sigma_G^2 + \sigma_E^2 \qquad (6\text{-}1)$$

In its simplest form, this model provides a starting point for understanding the quantitative genetics of complex traits. For example, σ_P^2 can be decomposed further into components representing the variance due to additive effects of genes at several loci (σ_A^2), dominance effects (σ_D^2), and **epistasis** (σ_I^2), while σ_E^2 can be decomposed into the variance due to specific measured environmental factors ($\sigma_{E\ \text{factor 1}}^2$) and that due to random, unmeasured environmental factors ($\sigma_{E\ \text{random}}^2$). *Broad sense heritability* refers to the proportion of the phenotypic variance attributable to all sources of genetic variance and is written as

$$h^2 = \sigma_G^2 / \sigma_P^2 \tag{6-2}$$

Narrow sense heritability refers to the proportion of the phenotypic variance attributable to only the additive genetic variance and is written as

$$h^2 = \sigma_A^2 / \sigma_P^2 \tag{6-3}$$

Generally speaking, at least initially, narrow sense heritability is more useful in characterizing the genetic effects of continuously distributed traits, such as stature or weight. Inheritance of such quantitative traits is likely to be influenced by a number of genes with small to moderate effects. For that reason, quantitative traits are often referred to as being **polygenic**. However, not all genes influencing a trait are likely to make the same contribution to the phenotypic variance of the trait. Also, since it is very difficult to identify genes explaining only a small proportion of the phenotypic variance of a trait (e.g., 5% or less), it is perhaps more practical to refer to most quantitative traits as being **oligogenic**, meaning that it is likely that a few genes with pronounced and identifiable effects of varying degrees are together responsible for most of the genetic contribution to the phenotypic variance of a trait. In most instances, h^2 estimates refer to narrow sense heritabilities. The variance components approach to decomposing the phenotypic variation exhibited in a quantitative trait briefly described here has its roots in the seminal work by Fisher[4] and is a powerful method for evaluating the different sources of variation contributing to the overall variance of a complex trait.

Genetic and Environmental Correlations

Quantitative genetics is much more than simply calculating h^2 estimates. Since it is well established that measures of growth and development have substantial and significant heritable components, the intellectual focus turns to the nature of the genetic regulation of growth and development. For example, significant phenotypic correlations often exist between different measures of growth and development. These phenotypic correlations may be due to pleiotropy, the joint effects of a gene or genes on different traits, or to shared environmental factors. In most cases, significant phenotypic correlations between two traits are due to both pleiotropy and shared environmental effects.

Just as the phenotypic variance of one trait can be decomposed into genetic and environmental variance components, so too the phenotypic correlation between two traits can be decomposed into genetic and environmental covariance components. Therefore, the phenotypic correlation between two traits is a function of the h^2 of each trait and the genetic and environmental correlations between them. This is written as

$$\rho_P = \sqrt{h_1^2}\sqrt{h_2^2}\rho_G + \sqrt{(1-h_1^2)}\sqrt{(1-h_2^2)}\rho_E \qquad (6\text{-}4)$$

where ρ_P is the phenotypic correlation, ρ_G is the genetic correlation, ρ_E is the environmental correlation, h_1^2 is the heritability of trait 1 and h_2^2 is the heritability of trait 2. If both traits have low heritabilities, the phenotypic correlation between them is largely due to the environmental correlation; whereas if both traits have high heritabilities, the phenotypic correlation between them is due largely to the genetic correlation.

As with phenotypic correlations, additive genetic and random environmental correlations range from –1.0 to 1.0. A genetic correlation of 1.0, for example, indicates complete positive pleiotropy between two traits. That is, there are genes that affect both of the traits being examined in the same manner. A genetic correlation significantly less than 1 indicates incomplete pleiotropy, meaning that the two traits are influenced to some extent by the same set of genes, but that other genes also are influencing the value of one or the other of the two traits. A genetic correlation of 0 between two traits indicates that the two traits have different genes controlling them. Finally, a negative genetic correlation indicates that the same set of genes operates in an opposite manner on the two traits. Similarly, the random environmental correlation is a measure of the direction and strength of the correlated response of two traits to nongenetic factors. If specific nongenetic factors have been identified and measured that influence the covariance of the two traits, however, then the environmental correlation can be decomposed into nonrandom and random components.

Multivariate quantitative genetic analyses, in which the heritabilities of two (or more) traits are estimated along with the genetic and environmental covariances between them, are powerful tools for investigating the nature of relationships between different aspects or measures of growth and development.

Applications of Genetic and Environmental Correlations to Longitudinal Data

Another topic of particular interest in the field of growth and development is the nature of the genetic control of a trait over time. For these types of analyses, it is necessary to have serial measurements of the trait or traits of interest. Serial measurements of traits separated by time are normally correlated to some degree, with higher phenotypic correlations often found over short intervals and lower phenotypic correlations found over longer intervals. *Canalization* is a familiar term to auxologists, referring to the tendency of a trait to follow a certain course or trajectory over time. The more highly canalized a trait, the higher are the phenotypic correlations between repeated measurements. From a genetic perspective, traits that are highly canalized and that show a relative insensitivity to changes in environmental conditions are likely to have relatively high heritabilities. The same genes, however, may or may not be influencing the trait to the same extent over the entire course of growth and development.

To test hypotheses concerning the genetic control of growth at different ages, the approach just discussed for the examination of two traits at one point in time is taken. In its simplest form, however, the "two traits" are now the same trait measured at two points in time. The genetic and environmental correlations between repeated measures of the trait at different ages are then calculated. This approach allows for disentangling shared genetic effects from shared environmental effects on a trait measured over the course of childhood.

The strength of a genetic correlation for a single trait with repeated measures is indicative of the degree of consistency or uniformity in the genetic control of the trait over time. For example, if a genetic correlation of 1.0 is found between stature measured at age 8 years and measured again at age 18, then it can be inferred that the genes influencing stature during the middle of childhood are the same as those that influence height in early adulthood. If a genetic correlation is obtained that is significantly lower than 1.0, however, then there is evidence that a different suite of genes control stature at ages 8 and 18 years. Similarly, the environmental correlation is a measure of the consistency or uniformity of the response of the trait to nongenetic factors over time.

Genotype-by-Environment Interaction

Understanding how genes interact with aspects of the physical and internal biological environment is essential for a complete understanding of the genetic architecture of complex traits. In studies where relatives live in different environments, genotype-by-environment (G × E) interactions can be examined using extensions of variance components methods for studying quantitative trait variation.

G × E interaction is likely an important influence on the variation observed among children in their growth and development, particularly in populations with a high prevalence of environmental factors known to negatively affect growth and development. The key to G × E interaction, however, is that not all children may respond to the same degree to such environmental factors, and a portion of that differential response at the phenotypic level may be due to genetic variation among individuals.

The simplest approach to modeling G × E interaction is to make the genetic variance in a trait a function of a dichotomous environmental variable. Examples of this could be the presence or absence of a particular disease in a child or high or low protein intake. Figure 6-1 shows a simple hypothetical depiction of the response of three genotypes at a locus to two different environments. In the presence of G × E interaction, the relationship between trait levels and specific genotypes vary as a function of the environment. In this case, trait levels in Environment 1 are substantially less variable compared to trait levels in Environment 2. For genotypes AA and AB, trait levels remain stable or decrease from Environment 1 to

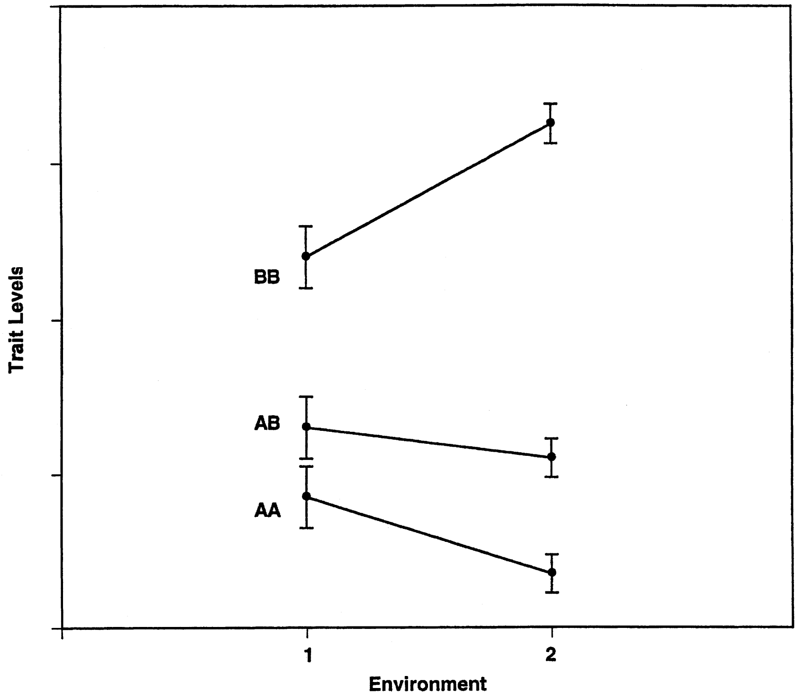

FIGURE 6-1 Hypothetical depiction of gene by environment interaction with the response of three genotypes at a locus to two different environments.

Environment 2. For genotype BB, trait levels increase from Environment 1 to 2. This example demonstrates how gene expression may vary under different environmental conditions.

In G × E analyses of the response of a quantitative trait, the variance components method is expanded and environment-specific additive genetic variances are estimated. For example, a large number of related children might be measured for a trait at a specific age and also tested for the presence of a particular infection at that age. If the additive genetic variances of the measured trait are not significantly different between infected and noninfected children, then that would be an indication that there is no G × E interaction between that trait and that infection at that age. If, on the other hand, the additive genetic variances of the measured trait are significantly different between infected and noninfected children, that would indicate a genetic basis to the differential response of the growth status of children to infection at that age. G × E interaction is also tested by examining the genetic correlation between the trait measured in different environments. A genetic correlation significantly different from 1.0 is another indication of G × E interaction. In the example here, a genetic correlation significantly less than 1.0 would indicate that the G × E interaction is due to an incompletely correlated genetic response of the trait in infected and noninfected children.

Genotype-by-Sex Interaction

Sexual dimorphism in the growth and development of children is well known, but the genetic basis of this sexual dimorphism is poorly understood. The approach for studying G × E interaction using related individuals living in different environments just described can be used to study genotype-by-sex (G × S) interactions. The rationale here being that the hormonal environments of males and females differ considerably and the expression of autosomal genes controlling a quantitative trait may be influenced by the sex-environment encountered.

In analyses of G × S interaction, the variance components method is again expanded. Additional parameters are estimated, the most important being sex-specific variance components and the genetic correlation between the sexes for the trait. G × S interaction is indicated by significantly different additive genetic variances for males and females or a genetic correlation between the sexes significantly less than 1.0.

G × S interaction analyses can be used to examine the genetic basis to the sexual dimorphism in measures of growth and development. The aim of G × S interaction analyses is to determine if the sexual dimorphism evidenced in a trait during childhood age is itself a heritable trait. In some families, for example, male and female children might not be very different in a measure of growth or development at a particular age, while in other families there might be significant differences between male and female relatives in that measure of growth or development at that age.

Genotype-by-Age Interaction

The nature of genetic influences on measures of growth and development may change over the course of childhood. As discussed earlier, the genetic correlation between a trait measured at two points in time can provide insight into the genetic control of a trait over time. If extensive longitudinal data from related children are available, genotype-by-age (G × A) interactions can be more rigorously examined. Like G × S interactions, G × A interactions are a type of G × E interaction. In this case, the "environment" is the age of the child at the time of the measurement of a trait. In these analyses, the additive genetic variance of a trait is modeled as a function of age. From these age-specific additive genetic variances, age-specific heritabilities of the trait can be determined. Also estimated are the additive genetic and environmental correlations between the trait measured across time.

G × A interaction is indicated by an additive genetic variance of a trait changing over a span of ages. This suggests that the genetic expression of a trait is dependent on the age of the child. G × A interaction also is indicated by a change in the genetic correlation between a trait measured over time. For example, a genetic correlation between a trait that decreases significantly from 1.0 over a span of ages indicates G × A interaction.

Identifying Genes Influencing Growth and Development

Once it has been determined that a trait has a significant heritability, interest turns to locating and identifying the actual genes that influence variation in the trait. Recent advances in molecular and statistical genetic methods make it possible to search for genes influencing complex traits. Unlike monogenic traits, which are influenced by a single gene with large effects, most complex traits are influenced by genes at a number of loci whose individual effects can be small. While understanding of monogenic growth disorders has significantly increased over the last few decades, understanding the genetics of normal variation in quantitative measures of growth and development has been a daunting task until more recently. Technological advances in molecular biology, not the least of which includes the sequencing of the human genome, and methodological advances in statistical genetics have made it possible to identify genes of small to moderate effect. There are two basic strategies to follow in the search for genes involved in the regulation of growth and development: population-based association studies or family-based quantitative trait linkage studies.

Association Studies

The first approach is the candidate gene association approach. Here, genes suspected to be physiologically involved in the trait are examined. For example, a sample of unrelated individuals are selected and genotyped for a polymorphism in or near the candidate gene. Simple statistical tests are then used to evaluate associations between marker genotype status and value of the trait. Carriers of a rare allele, for example, may have a mean value for the trait that is significantly different than the mean value of the trait in those who do not have a copy of that allele. Association studies have an obvious appeal. They are simple and straightforward compared to the analysis of marker genotype and quantitative trait data from family members.

There is a major problem with association studies, however, that has become evident in the last few years, as greater knowledge has been gained regarding **linkage disequilibrium**. Two loci are in equilibrium when alleles at the two loci are randomly associated with each other. If the relationship between the loci is not random, then linkage disequilibrium is present. Unfortunately, linkage disequilibrium can occur for a number of reasons, including new mutations, genetic drift, and in the presence of selection. Additionally, significant associations can be due to heterogeneity in the population sampled. This occurs when population subgroups differ systematically in both allele frequencies and levels of the quantitative trait of interest. The main problem with association studies, however, is that disequilibrium cannot be predicted. Two loci may be very close to each other and yet be in equilibrium. Conversely, two loci may be relatively far apart from each other and yet be in disequilibrium. There is no sure way to know that the marker that has been typed is in disequilibrium with the trait that has been measured. If it is known a priori that the marker typed is in fact a functional polymorphism (that is, there is a measurable difference among marker genotypes in gene expression, such as one genotype results in much lower levels of a particular protein compared to the other genotypes), however, then association studies might be a viable strategy to pursue if familial data are unavailable.

Quantitative Trait Linkage Analysis

The second approach to gene discovery involves linkage mapping. Linkage studies require a great deal of planning prior to their initiation to obtain maximal statistical power to detect genes of modest to moderate effect. The premise behind linkage analysis is that, if two loci are physically located close to each other, then alleles at these loci will be more likely to be inherited together. In this sense, the loci are said to be linked. As the distance between loci increases, the probability that alleles at these loci will **cross over** or **recombine** during meiosis increases. Through investigation of the frequency of recombination events among genetic markers, one can localize to chromosomal regions loci influencing quantitative variation of a trait. Once a region has been identified, then more precise molecular mapping techniques can be used to more clearly define regions of interest and to identify functional polymorphisms.

In recent years there have been many advances in linkage analysis as applied to complex traits. Most recently, allele-sharing methods have gained prominence for quantitative traits. The key premise behind allele-sharing methods is the concept of **identity by descent** (IBD). In comparisons between relatives, two alleles that are structurally identical are said to have **identity by state** (IBS); alleles that are structurally identical and inherited from a common ancestor (e.g., two siblings getting the same allele from their mother) are further classified as IBD. A pair of relatives can share either 0, 1, or 2 alleles IBD at any given marker locus. The likelihood of their sharing 0, 1, or 2 alleles IBD is contingent on their coefficient of kinship. Linkage between a **quantitative trait locus** (QTL) and a marker exists in chromosomal regions when pairs of relatives who are more phenotypically similar share more alleles at a marker locus than pairs of relatives who are more phenotypically dissimilar.

The power to detect and localize QTLs is a function of several factors. The most important consideration is the strength of the genetic effect. Traits that are highly heritable will have a higher probability of being mapped than those of low to modest heritability. Also, as in any statistical analysis, sample size is of importance, but in linkage studies, other aspects of the sample are equally important. The family structure of the sample is especially important. Having many families is good, but having fewer more complex extended pedigrees yields increased statistical power because of the greater number and variety of relationships among relatives.

STUDY DESIGNS

A number of different study designs can be used to examine the genetics of complex traits. Each study design has certain advantages and disadvantages. This section describes some of the major types of study designs used by genetic epidemiologists to study complex quantitative traits.

Twin Studies

Over the years, studies of twins have been useful in establishing the familial aggregation of many complex traits. In its basic form, the twin model compares phenotypic differences between two classes of twins, monozygotic (MZ) and dizygotic (DZ). MZ twins share 100% of their genetic makeup, while DZ twins on average share only half of their genetic makeup (i.e., on the genetic level they are the same as any other pair of full siblings). Because of this, phenotypic differences observed between MZ twins are assumed to be the result of environmental factors only, while phenotypic differences between DZ twins are considered to be due to differences in both genes and environmental exposure. Therefore, by calculating phenotypic correlations in groups of MZ and DZ twins and comparing them, assumptions can be made about the degree of genetic control of different traits.

One important assumption in the classical twin study design is that both MZ and DZ twin pairs are equally likely to share a common environment. This assumption may not be valid, however, because MZ twins are often more likely to share common activities, foods, and other aspects of the environment to a greater extent than DZ twins. Because there is no fully satisfactory way to separate shared genetic and environmental effects, studies of twins often yield inflated h^2 estimates (indeed, there are some published h^2 estimates from twin studies that are greater than 1, an estimate that is biologically impossible).

The twin study design is especially problematic if the focus of the study is a growth-related outcome. Twin births are physiologically different from singleton births due to competition over maternal resources during pregnancy. Fetal growth rates among twins may be considerably discordant, and the postnatal growth of twins is often different from that of siblings from singleton births (e.g., catch-up growth in twins).

Nuclear Families

Another commonly used study design is the nuclear family design. In this study design, correlations between the various classes of first-degree relatives in a nuclear family are estimated. These include parent-offspring, sibling-sibling, and spouse-spouse correlations. Heritabilities can be estimated from these different familial correlations. Heritability estimates calculated from nuclear family data, however, are subject to inflation, due to the effects of shared environmental factors, such as diet and lifestyle, among family members living in a single residence. Given this, heritabilities are often adjusted by taking into account the degree of spousal correlation in the family. It is assumed that any correlation found between spouses is the result of shared environmental factors. Such spousal correlations may depend on the length of time that the couple has been married. Also, such spousal correlations may be the result of **assortative mating**.

A number of practical considerations must be taken into account in studies of nuclear family members apart from those just mentioned. For example, it is sometimes difficult to obtain information about certain life events because they are often separated in time by a generation—20–30 years may be needed to collect growth measures of the children of parents who were measured when they were children. Also, generational differences in growth may be due to secular trends. This may effectively reduce the heritability of certain traits by diminishing the degree of phenotypic correlation observed. These two problems can be eliminated by examining only sibling correlations, but the problem of shared environment remains.

Extended Pedigrees

The study design that offers the most promise for elucidating the genetic architecture of complex traits is the extended family approach. This approach involves collecting information from all available family members and estimating phenotypic correlations between all relatives of varying degrees. By sampling members outside of the immediate nuclear family, many of the problems encountered with shared environmental effects in other study designs are minimized, because family members come from a number of different households. This results in more accurate and reliable h^2 estimates. In addition, by sampling members in different households who thereby live in potentially different environmental circumstances, there is opportunity to investigate the effects of G × E interaction. With regard to the study of growth and development, large extended pedigrees will include substantial numbers of related children who are of approximately the same age. This enables analyses to proceed very quickly after the initiation of data collection.

There are a few practical drawbacks to this approach, however. The single most important consideration is that the methods involved in calculating quantitative genetic parameters are computationally intensive. This, however, is much less of an obstacle as computer technologies continue to progress. Indeed, the incredible advances in computer technology over the last 20 years has made the statistical genetic analyses of data from large pedigrees tractable. Also, collecting data from large numbers of individuals of varying ages requires a great deal of planning, effort, and research funding.

STUDIES OF THE GENETICS OF GROWTH AND DEVELOPMENT

The preceding sections introduced a number of basic terms and concepts necessary for understanding genetic epidemiological approaches to growth and development. This section provides a brief overview of numerous studies on genetic factors in growth and development that have been conducted over the last century. The review presented here provides a sampling of a significant part of this literature, focusing on studies of height, birth weight, menarche, and skeletal development.

Population Differences in Growth and Development

There is considerable variation across populations in growth in height, weight, and other body dimensions, as well as in the tempo and timing of maturation.[5] For example, mean adult height varies from approximately 150 cm for males in the shortest populations on earth (e.g., Mbuti pygmies of central Africa) to over 180 cm for males in northern European populations. These long-standing observations of racial or ethnic differences in growth and development rendered support for the notion that genetic factors are likely involved. The degree to which genetic factors influence growth and development cannot be addressed, however, by the simple comparison of measures of growth and development traits across populations. The populations compared often are exposed to vastly different environments, and the shortest and smallest populations also tend to have the poorest economic status, while the tallest populations tend to be from industrialized nations. Between-population differences may be due to differences in both genetic and environmental factors, whose relative importance is often confounded. For example, evidence of secular trends in stature and pubertal maturation,[5] and the degree of similarity for stature in high socioeconomic status groups from various parts of the world (e.g., Martorell, Mendoza, and Castillo[6]), argue that a significant part of interpopulation variation in growth and development is due to environmental factors.

Family Studies of Growth and Development

Population comparisons provide only indirect evidence of a connection between genetic factors and phenotypic variation in growth and development. In contrast, family studies within populations can clearly define the relationships between genes and growth, because environmental and genetic sources of variation can be explicitly modeled with these designs. Table 6-1 summarizes published familial correlations and the heritability estimates for birth weight, height, weight, and other anthropometric measures, as well as age at menarche in females from a selection of family studies from diverse populations. While Table 6-1 does not contain an exhaustive listing of all published findings, the studies listed were published in widely circulated journals and represent the range of findings reported in the literature.

Several general comments can be made regarding these investigations. First, the studies to date are based almost entirely on first-degree familial correlations. That is, they are based on either nuclear family or twin pair designs. And, as discussed already, there are important concerns when studying only first-degree relatives, particularly when studying growth and development. These concerns include

TABLE 6-1 Heritability Estimates of Anthropometrics During Childhood and Adolescence

Trait	Reference	Population	Design Family Structure	Sample Size	Familial Correlations	Heritability or Variance Estimates
Birth weight						
European	Clausson, Lichtenstein, & Cnattinigius, 2000[45]	Sweden	Cross-sectional Twins	868 MZ 1141 DZ		$h^2 = 0.25–0.40$
	Nance et al., 1983[46]	United States	Cross-sectional Nuclear, twins	Offspring of 385 twin pairs	$r_{\text{sibs}} = 0.48$ $r_{\text{halfsibs-mo}} = 0.31$ $r_{\text{halfsibs-fa}} = -0.03$	
	Penrose, 1954[8]	United Kingdom	Cross-sectional Nuclear			Fetal genetic factors: 18% Maternal genetic factors: 20% Environmental factors: 62%
Non-European	Morton, 1955[47]	Japan	Cross-sectional Nuclear, twins		$r_{\text{twins}} = 0.56$ $r_{\text{sibs}} = 0.52$ $r_{\text{halfsibs-mo}} = 0.58$ $r_{\text{halfsibs-fa}} = 0.10$	
Height						
European	Susanne, 1977[48]	Belgium	Cross-sectional Nuclear	125 families	$r_{\text{pc}} = 0.51$	$h^2 = 0.82$
	Solomon, Thompson, & Rissanen, 1983[49]	Finland	Cross-sectional Nuclear	2869 individuals		$h^2 = 0.58$
	Mueller, 1976[11]	United States, United Kingdom, West Europe, East Europe	Cross-sectional Nuclear	Varied	$r_{\text{pc}} = 0.37$ (average)	

Malina, Mueller, & Holman, 1976[50]	United States White and black	Cross-sectional Nuclear	422 black families 384 white families		$h^2 = 0.49$ (white) $h^2 = 0.37$ (black)
Garn, Bailey, & Cole, 1976[51]	United States	Cross-sectional (adopted/biological siblings)	6726 biological, 504 adoptive parent-offspring pairs	$r_{\text{adopted sibs}} = 0.29$ $r_{\text{biological sibs}} = 0.35$	
Fischbein, 1977[52]	Sweden	Longitudinal Twins	94 MZ 233 DZ	$r_{\text{MZ}} = 0.9$ $r_{\text{DZ}} = 0.6–0.7$	
Fischbein and Nordqvist, 1978[53]	Sweden	Longitudinal Twins Age: 10–16 yr (growth curve concordance)	94 MZ 133 DZ	Average growth profile similarity within twin pair: $r_{\text{MZ}} = 0.85$ $r_{\text{DZ}} = 0.54$	
Byard, Guo, & Roche, 1993[54]	United States	Longitudinal Nuclear (height curve parameters)	228 families	Age at TO: $r_{\text{pc}} = 0.17$, $r_{\text{sibs}} = 0.32$ TOV: $r_{\text{pc}} = 0.26$, $r_{\text{sibs}} = 0.35$ Age at PHV: $r_{\text{pc}} = 0.22$, $r_{\text{sibs}} = 0.35$ PHV: $r_{\text{pc}} = \text{ns}$, $r_{\text{sibs}} = 0.32$	
Towne et al., 1993[36]	United States	Longitudinal Nuclear/extended (height curve parameters) Age: 0–2 yr	569 individuals		Recumbent length at birth: $h^2 = 0.83$ Velocity 0–2 yr: $h^2 = 0.67$ Acceleration 0–2 yr: $h^2 = 0.78$

(continues)

TABLE 6-1 *(continued)*

Trait	Reference	Population	Design Family Structure	Sample Size	Familial Correlations	Heritability or Variance Estimates
Height *(cont.)*						
European *(cont.)*	Wilson, 1976[9]	United States	Longitudinal Twins Age: 0–4 yr	159 MZ 195 DZ	$r_{MZ} = 0.58$ (birth)–0.94 (age 4) $r_{DZ} = 0.69$ (birth)–0.61 (age 8)	
	Beunen et al., 1998[16]	Belgium	Longitudinal Twins Age:10–18 yr	99 twin pairs		Age at TO: $h^2 = 0.93$ TOV: $h^2 = 0.90$ Age at PHV: $h^2 = 0.92$ PHV: $h^2 = 0.89$
	Welon & Bielicki, 1971[13]	Warsaw, Poland	Longitudinal Nuclear Age: 8–18 yr	496 parent-child pairs	$r_{\text{parent-son}} = 0.36$ (8 yr), 0.43 (18 yr) $r_{\text{parent-dau}} = 0.54$ (8 yr), 0.59 (18 yr)	
	Vandenberg & Falkner, 1965[55]	United States	Longitudinal Twins (stature curve parameters) Age: 0–6 yr	29 MZ 31 DZ	Concordance between MZ and DZ twins: MZ = DZ initial value (birth) MZ < DZ (velocity) MZ < DZ (acceleration)	
	Hauspie et al., 1994[56]	Poland	Longitudinal Twins (stature curve parameters)	44 MZ 42 DZ		Age at TO: $h^2 = 0.49$ Age at PHV: $h^2 = 0.74$ PHV: $h^2 = 0.76$

Non-European	Roberts, Billewicz, & McGregor, 1978[57]	West Africa	Cross-sectional Nuclear Full and half sibs	276 sibships		Fa-child: $h^2 = 0.61$ Mo-child: $h^2 = 0.85$ Midparent-child: $h^2 = 0.65$ Full sibs: $h^2 = 0.81$ Paternal half-sibs: $h^2 = 0.56$ (“best” h^2 estimate)
	Mueller & Titcomb, 1977[58]	Colombia	Cross-sectional Nuclear Age: 7–12 yr	403 families	$r_{\text{mo-child}} = 0.28$ $r_{\text{fa-child}} = 0.27$	$h^2 = 0.49$ (boys) $h^2 = 0.47$ (girls)
	Devi & Reddi, 1983[59]	India	Cross-sectional Nuclear	436 families	$r_{pc} = 0.34$ $\mathrm{r}_{\text{sibs}} = 0.33$	$h^2 = 0.65$
	Kaur & Singh, 1981[60]	India	Cross-sectional Nuclear	82 families	$r_{pc} = 0.48$	$h^2 = 0.92$
	Sharma et al., 1984[61]	India	Cross-sectional Nuclear/twins	151 sibs 98 DZ 44 MZ	$r_{\text{sibs}} = 0.30$ $r_{DZ} = 0.59$ $r_{MZ} = 0.98$	
	Mueller, 1976[11]	Colombia, Africa, Peru, New Guinea, Japan	Cross-sectional Nuclear	Varied	$r_{pc} = 0.29$ (average)	
Weight						
	Susanne, 1977[48]	Belgium	Cross-sectional Nuclear	125 families	$r_{pc} = 0.34$	$h^2 = 0.64$
	Mueller & Titcomb, 1977[58]	Colombia	Cross-sectional Nuclear	403 families	$r_{\text{mo-child}} = 0.36$ $r_{\text{fa-child}} = 0.31$	$h^2 = 0.16$ (boys) $h^2 = 0.21$ (girls)
	Kaur & Singh, 1981[60]	India	Cross-sectional Nuclear	82 families	$r_{pc} = 0.34$	$h^2 = 0.39$

(continues)

TABLE 6-1 *(continued)*

Trait	Reference	Population	Design Family Structure	Sample Size	Familial Correlations	Heritability or Variance Estimates
Weight *(cont.)*						
	Garn et al., 1976[51]	United States	Cross-sectional (Adopted/ biological siblings)	6726 biological, 504 adoptive parent-offspring pairs	$r_{\text{adopted sibs}} = 0.18$ $r_{\text{biological sibs}} = 0.27$	
	Wilson, 1976[9]	United States	Longitudinal Twins Age: 0–4 yr	159 MZ 195 DZ	$r_{MZ} = 0.61$(birth)–0.86 (age 4) $r_{DZ} = 0.68$ (birth)–0.55 (age 8)	
	Fischbein, 1977[52]	Sweden	Longitudinal Twins Age: 10–16 yr	94 MZ 233 DZ	$r_{MZ} = 0.8$–0.9 from 10–16 yr $r_{\text{DZ-boys}} = 0.6$–0.7 from 10–16 yr $r_{\text{DZ-girls}} = 0.7$ (10 yr)–0.2 (16 yr)	
	Fischbein & Nordqvist, 1978[53]	Sweden	Longitudinal Twins Age: 10–16 yr Growth curve concordance	94 MZ 133 DZ	Average growth profile similarity within twin pair: $r_{MZ} = 0.79$ $r_{DZ} = 0.22$ (girls)–0.53 (boys)	
Biacromial breadth						
	Sharma et al., 1984[61]	India	Cross-sectional Nuclear/twins	610 individuals	$r_{\text{sibs}} = 0.32$ $r_{DZ} = 0.56$ $r_{MZ} = 0.95$	

	Devi & Reddi, 1983[59]	India	Cross-sectional Nuclear	436 families	$r_{pc} = 0.30$ $r_{sibs} = 0.37$	$h^2 = 0.49$
	Kaur & Singh, 1981[60]	India	Cross-sectional Nuclear	82 families	$r_{pc} = 0.38$	$h^2 = 0.75$
	Mueller & Titcomb, 1977[58]	Colombia	Cross-sectional Nuclear 7–12 yr	403 families	$r_{mo\text{-}child} = 0.33$ $r_{fa\text{-}child} = 0.32$	$h^2 = 0.63$ (boys) $h^2 = 0.40$ (girls)
	Susanne, 1977[48]	Belgium	Cross-sectional Nuclear	125 families	$r_{pc} = 0.33$	$h^2 = 0.58$
Biiliac breadth						
	Ikoma et al., 1988[62]	Japan	Cross-sectional Nuclear	3632 individuals	$r_{sibs} = 0.30$ $r_{pc} = 0.27$	$h^2 = 0.54$–0.55
	Devi & Reddi, 1983[59]	India	Cross-sectional Nuclear	436 families	$r_{pc} = 0.18$ $r_{sibs} = 0.18$	$h^2 = 0.34$
	Susanne, 1977[48]	Belgium	Cross-sectional Nuclear	125 families	$r_{pc} = 0.49$	$h^2 = 0.73$
Upper arm circumference						
	Mueller & Titcomb, 1977[58]	Colombia	Cross-sectional Nuclear 7–12 yr	403 families	$r_{mo\text{-}child} = 0.37$ $r_{fa\text{-}child} = 0.32$	$h^2 = 0.20$ (boys) $h^2 = 0.34$ (girls)
	Sharma et al., 1984[61]	India	Cross-sectional Nuclear/twins	162 sibs 98 DZ 44 MZ	$r_{sib} = 0.26$ $r_{DZ} = 0.52$ $r_{MZ} = 0.95$	
	Devi & Reddi, 1983[59]	India	Cross-sectional Nuclear	436 families	$r_{pc} = 0.26$ $r_{sibs} = 0.24$	$h^2 = 0.46$
	Kaur & Singh, 1981[60]	India	Cross-sectional Nuclear	82 families	$r_{pc} = 0.23$	$h^2 = 0.24$
	Susanne, 1977[48]	Belgium	Cross-sectional Nuclear	125 families	$r_{pc} = 0.30$	$h^2 = 0.50$

(continues)

TABLE 6-1 *(continued)*

Trait	Reference	Population	Design Family Structure	Sample Size	Familial Correlations	Heritability or Variance Estimates
Age at menarche						
	Damon et al., 1969[21]	United States	Retrospective Nuclear	78 mo-dau pairs	$r_{\text{m-dau}} = 0.24$	
	Orley, 1977[63]	Hungary	Retrospective Nuclear	550 mo-dau pairs	$r_{\text{mo-dau}} = 0.25$	
	Kaur & Singh, 1981[60]	India	Retrospective Nuclear	72 mo-dau pairs	$r_{\text{m-dau}} = 0.39$	
	Meyer et al., 1991[23]	Australia	Retrospective Twins	1178 MZ 711 DZ	$r_{\text{MZ}} = 0.71$ $r_{\text{DZ}} = 0.22$	$h^2 = 0.17$ (additive effects) $d^2 = 0.54$ (dominance effects)
	Malina, Ryan, & Bonci, 1994[24]	United States	Retrospective Nuclear University athletes	109 mo-dau pairs 77 sib pairs	$r_{\text{mo-dau}} = 0.25$ $r_{\text{sib}} = 0.44$	
	Brooks-Gunn & Warren, 1988[25]	United States	Retrospective Nuclear family Age: 14–17 yr (daughters)	307 mo-dau pairs	$r_{\text{mo-dau}} = 0.26$ (nondancers) $r_{\text{mo-dau}} = 0.32$ (ballet dancers)	
	Loesch et al., 1995[26]	Poland	Longitudinal Twins (all female) Age: 0–18 yr (examined genetic correlations among maturity traits)	95 MZ 97 DZ		h^2 (raw) = 0.95 $h^2 = 0.44$ (unique genetic effects) $h^2 = 0.53$ (shared genetic effects with skeletal maturity)

Abbreviations: Mo = mother; Fa = father; Dau = daughter; MZ = monozygotic twins; DZ = dizygotic twins; r_{pc} = parent-child correlation; r_{sib} = sibling correlation; TO = "takeoff" (height velocity minimum); TOV = velocity at "takeoff" (height velocity minimum); PHV = peak height velocity.

secular trends that may reduce correlations between parents and offspring, and the shared environments of siblings, especially twins, that may inflate correlations between them. Second, specific environmental sources of variation, such as diet and disease, usually have not been incorporated into the analyses. Not accounting for the variance in a trait attributable to such environmental factors can lead to erroneous estimation of the heritability of the trait. Third, the majority of studies have focused solely on height at a given point in time (mostly adult height). A much smaller number of studies have examined variation in other anthropometrics. Fourth, the majority of studies are based on cross-sectional data. Only a very few studies have longitudinal growth and development data from related individuals that permit examination of genetic influences on patterns of change in height, weight, and other measures over time. And fifth, almost all of the studies have focused solely on the *magnitude* of genetic effects. There are very few multivariate quantitative genetic analyses of measures of growth and development; analyses of genotype-by-environment, -sex, or -age interactions; association studies; or linkage analyses.

Birth Weight

The genetics of prenatal growth has largely been approached by examining the heritability of birth weight. Initially, genetic influences on birth weight were deduced from the known effects of quantitative changes in chromosomes. For example, supernumerary autosomes (trisomy 21, 18, and 13) and abnormal numbers of X chromosomes (as in Turner syndrome) all result in growth retardation. Formal quantitative genetic analyses of birth weight find somewhat lower heritability estimates than for body weight and length in postnatal life, which are both highly heritable (see later). Assessment of genetic influences on birth weight is complicated, however, because prenatal growth (at least as measured by birth weight) is influenced by both the genetic makeup of the fetus and the maternal intrauterine environment, and there is no fully satisfactory way to partition these two sources of variation. Therefore, not surprisingly, estimates of the influences of fetal genes, maternal genes, nongenetic maternal factors, and random environmental effects on fetal growth vary considerably across studies. The role of fetal genes varies from 0 to 50%, maternal factors from 27 to 50%, and random environmental factors from 8 to 43% in the variation in birth weight.[7]

A classic study by Penrose[8] attempted to partition the variance in birth weight among fetal genes, maternal genes, nongenetic maternal factors, and random environmental effects. He concluded that fetal genes accounted for approximately 18% of the phenotypic variance, while "maternal factors" (a combination of both genetic and uterine environment) explained approximately 40% of the phenotypic variance. The importance of uterine environment in the control of prenatal growth is also demonstrated by the changes in twin correlations from birth onward (e.g., Wilson[9]). Intrapair differences in the birth weight of MZ twins are often significant at birth (tending to be larger than differences between DZ twins), because MZ twins compete for placental resources. Differences in weight between MZ twins decreases over time. By 3 years of age, the MZ twin correlation is about 0.80–0.90 and the DZ twin correlation is about 0.40–0.50.

A problem with the use of birth weight as a measure of prenatal growth is that it represents growth status at a variety of maturational ages depending on gestational age. Most studies of the genetics of birth weight have not controlled for gestational age. This flaw has likely led to underestimates of genetic influences. Indeed, using a variance components method for pedigree data and modeling a gestational age covariate effect, we found a high heritability of birth weight in the Fels Longitudinal Study population ($h^2 = 0.80$; Demerath et al., unpublished results). Continued work along these lines will help identify specific factors influencing fetal growth and development. However, progress depends on measurement strategies that better capture the process of fetal development (e.g., serial ultrasound biometry).

Height

Data from nearly 4000 individuals in 1100 nuclear families in England analyzed by Pearson and Lee[10] provide perhaps the earliest evidence for the inheritance of height. In this landmark study, Pearson and Lee found a significant correlation between spouses (0.28), which shows positive assortative mating for height, but higher correlations between siblings (0.54) and between parents and offspring (0.50). Since the expected correlation between full siblings and between parents and offspring would be 0.50 if the h^2 of the trait was 1.0, they concluded that the population variation in height was highly determined by genetic factors. These early results have been corroborated by hundreds of subsequent family studies. In populations around the world, the estimates of the h^2 of height range from 0.6 to above 0.9, clearly showing that height is a highly heritable trait.

In a review of 24 studies of parent-child correlations of height and weight, however, Mueller[11] indicated that population estimates of heritability tend to be systematically lower in developing countries than affluent countries. There are a number of reasons why this might be so. As mentioned earlier, according to classic quantitative genetic theory, the heritability of height or any trait is a function of the population in which the estimate is made, as well as of the trait itself. Heritability estimates tend to be higher if there is positive assortative mating (i.e., a significant phenotypic correlation between parents). And indeed, assortative mating for height has been found in European populations more frequently than in non-European populations. Also, non-European populations in the developing world tend to live under more nutritional and disease stress than European populations. In these populations, such environmental factors have the potential to affect a given trait more than in affluent populations. Since heritability is the proportion of variance due to genetic influences, a larger proportion of environmentally induced variation reduces the heritability. Additionally, many non-European populations are experiencing rapid economic change, which results in the growth environments of children differing quite markedly from that of their parents, thus decreasing parent-offspring correlations and the estimate of total variation attributable to genes.

Other Anthropometric Measurements

Whereas the heritability of skeletal length (e.g., height, sitting height) tends to be high, the h^2 of skeletal breadth (e.g., biiliac and biacromial diameters) tends to be somewhat lower, averaging between 0.4 and 0.8. In turn, skeletal breadth tends to have higher heritability than weight, circumference, and skinfolds. It has been assumed that soft-tissue traits are more easily altered by the changing nutritional environment of individuals than skeletal tissues, which respond less quickly to changes in nutritional status, and, as a result, have a greater proportion of their variance explained by environmental, rather than genetic, factors. Nonetheless, growth status in all anthropometrics has been shown to have a significant heritable component.

Longitudinal Studies

As mentioned earlier, the vast majority of family studies of growth are cross-sectional. Only a few studies have longitudinal growth and development data from related children that permit genetic analyses of the processes of growth and development. Some of these longitudinal studies of the genetics of growth, for example, examined changes in parent-child or sibling correlations from age to age. Reports from the Fels Longitudinal Study,[12] Poland,[13] and elsewhere[14,15] indicated that parent-child correlations for height increase during the first 4 years of life, decrease during adolescence (when heterogeneity of maturational tempo disrupt familial similarity), and subsequently rise above the prepubertal level.

Modern longitudinal studies of growth and development use various growth curve fitting methods to pinpoint maturational events, particularly of changes in the tempo of growth in stature, and then examine growth curve parameters in genetic analyses. For example, Buenen et al.[16] report high heritability estimates for the ages at takeoff and peak height velocities, and the heights at those ages. Similar analyses of Fels Longitudinal Study data are discussed in more detail later.

Maturation

Not only is physical size heritable, but the timing and tempo of maturation also are significantly controlled by genes. A number of early studies of dental development found that radiographic measures of the timing of tooth formation (calcification) and dental emergence were more highly correlated within MZ twin pairs than DZ twin pairs, suggesting a heritability of 0.85–0.90.[17] Also, the number and pattern of dental cusps were found to be under genetic control. The rate of skeletal maturation has been compared in siblings over time in several reports, with the general finding being that there is a great deal of similarity between sibs in the age of ossification onset of bones in the hand and foot. The general pattern of skeletal maturation (i.e., the tendency to be an “early” or “late” maturing individual) also suggests that the tempo of development is highly heritable, with sib-sib correlations of 0.45.[18]

The process of maturation is commonly believed to be controlled, at least partially, by genes independent from those controlling final size. This conjecture stems from the observation that siblings may reach identical height even though they differed in the timing of maturational events.[19] Further and more widespread use of the multivariate quantitative approaches discussed previously, in which genetic and environmental correlations between different traits may be calculated, allows for greater understanding of the extent of shared genetic and nongenetic factors underlying growth and development traits.

Age at menarche is one of the most studied developmental traits. Many early studies suggested that age at menarche has a genetic basis (e.g., Boas[20]). The mother-daughter and sister-sister correlations in the age at menarche were close to 0.50, indicating a high degree of genetic determination of age at menarche. These and later studies, however, relied primarily on recalled ages at menarche, and thus recall bias (greater in mothers than in daughters) is introduced into these estimates. Subsequent work has confirmed a strong genetic influence on age at menarche.[21–25] Beyond the documentation of the magnitude of genetic influences on menarche, a recent study sought to decompose the known relationships between skeletal development, BMI, and the onset of menarche into their shared genetic and environmental components.[26] Further work of this type will improve our understanding of the orchestration of changes in body size and maturation.

EXAMPLES FROM THE FELS LONGITUDINAL STUDY AND THE JIRI GROWTH STUDY

This section highlights some of the topics discussed in the preceding sections through examples of genetic analyses conducted over the years in the Fels Longitudinal Study and those currently underway in the recently established Jiri Growth Study.

Fels Longitudinal Study

The Fels Longitudinal Study began in 1929 in Yellow Springs, Ohio. It was one of several longitudinal studies of child growth and development initiated in the United States between the end of World War I and the start of the Great Depression, and it is the only one that has survived to today. Although the Fels Longitudinal Study did not begin with an interest in genetics, familial data began to be collected soon after the study began. Most of the mothers who enrolled their children in the early years of the study had more children later, and many of those children subsequently became participants. Also, a set of monozygotic, dichorionic triplets was recruited early in the study specifically to examine their similarities in growth and development. Another set of triplets and a few twin pairs also were recruited in later years. Over time, other relatives were incorporated into the study, the first of these being the offspring of study participants. The Fels

Longitudinal Study today has more than 1000 participants with extensive serial data from infancy and cross-sectional data from more than 2000 of their relatives. These individuals represent about 200 kindreds consisting of both nuclear and extended families.

The description of the Genetics Program of the Fels Longitudinal Study written by its first director, Lester W. Sontag, is remarkable for its modern sounding tone.[27] Sontag noted that many aspects of growth and development are likely to have significant genetic determination but are influenced by environmental factors as well. He noted that the study included many families with two or more children, and that these "constitute the material for the study of inheritance of growth patterns as well as of metabolic characteristics."

For example, the set of monozygotic, dichorionic triplets just mentioned were the subject of three early reports that described their similarities in physical and mental traits as young children, striae in their bones, and the onset of ossification from infancy through pubescence.[28–30] Soon after the triplet's 18th birthday,[31] Reynolds and Schoen reported a description of their growth patterns. A paper by Reynolds[32] is especially noteworthy because it used familial data from different types of relatives to examine the effects of degree of kinship on patterns of ossification. Included in this analysis were the set of identical triplets, as well as 3 pairs of identical twins, 22 pairs of siblings, 8 pairs of first cousins, and 18 unrelated children. Reynolds found that close relatives were very similar in pattern of ossification, distant relatives less so, and unrelated even less similar.

A series of studies from the late 1950s to the late 1960s by Garn and colleagues used data from siblings, parents, and offspring to examine patterns of familial correlations in traits pertaining especially to dental and skeletal maturation. An example of the analyses and sample sizes from this period is provided by Garn, Lewis, and Kerewsky,[33] who examined ossification data from radiographs of the hand-wrist and chest for 72 parent-child pairs, 318 sibling pairs, 4 pairs of dizygotic twins, and 4 pairs of monozygotic twins. Since these were serial data taken at half-yearly intervals from ages 1 to 7, there were 1211 pairings of parent-child data, 6690 pairings of sibling data, 102 pairings of data from dizygotic twins, and 176 pairings of data from monozygotic twins. They concluded that, "In these well-nourished . . . Ohio-born white children, genes appear to account for a major proportion of ossification variance during growth." These investigators also examined the genetics of various dental traits, including the timing of stages of dental development,[17] tooth morphology,[34] and the appearance of discrete dental traits.[35] The influence of familial factors on growth in body size also were examined.[12]

Genetic analyses of growth and development data from the Fels Longitudinal Study data have had a resurgence in recent years. This is due largely to advances in statistical genetic methods that maximize the amount of information available in longitudinal data from large numbers of relatives of varying degrees of relationship to one another, as well as advances in molecular genetic methodology that allow for relatively low-cost genotyping. For example, Towne et al.[36] fitted a three-parameter function to serial recumbent lengths from 569 infants in order to characterize each individual's unique pattern of growth during infancy. Figure 6-2 shows the growth curves of two infant boys who differ in their patterns of growth. Boy #1 started out in life shorter than Boy #2, but had a rate of increase in recumbent length that was much greater than that of Boy #2. Both boys, however, experienced about the same amount of growth (~42 cm) from birth to age 2 years. In this study, substantial h^2 estimates of 0.83 for recumbent length at birth, 0.67 for rate of increase in length, and 0.78 for a parameter describing the curvilinear shape of growth in recumbent length from birth to 2 years were found.

Towne et al.[37] used the triple logistic model of Bock et al.[38] to fit growth curves to serial stature data from 471 Fels Study participants, age 2–22 years, representing 188 kindreds, to conduct a multivariate quantitative genetic analysis of different parameters of the pubertal growth spurt. Figure 6-3 shows the growth and velocity curves of two girls with visibly different growth patterns. Girl #1 was only 9.37 years old when she was at the peak of her pubertal growth spurt, whereas the age at peak height velocity of Girl #2 was 13.09 years. At the time of peak height velocity, Girl #1 was shorter than Girl #2 (141.1 cm vs. 156.5 cm), which is expected given her younger age at peak height velocity; but at the age at peak height velocity, Girl #1 had a higher rate of growth than Girl #2 (8.8 cm/yr vs. 6.4 cm/yr). By the end of their growth, Girl #1 was a petite woman (158.5 cm) while Girl #2 was somewhat taller than average (170.6 cm). Highly significant h^2 estimates—on the order of 0.85 for age at peak height velocity, 0.61 for growth rate at peak height

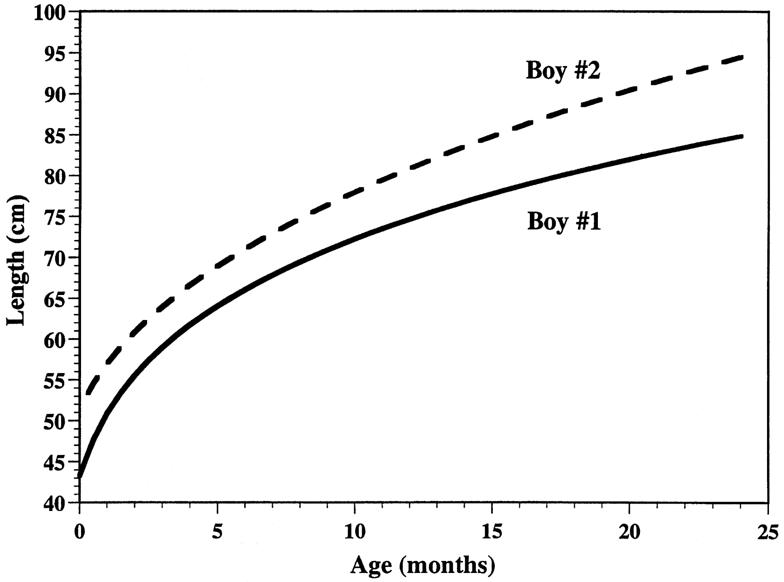

FIGURE 6-2 Height distance curves for two boys with differing growth patterns between birth and 24 months old.

velocity, and 0.96 for stature at the age of peak height velocity—were found. Especially interesting was the finding of additive genetic correlations between these pubertal growth spurt parameters that were significantly lower than 1.0, suggesting incomplete pleiotropic effects of genes on different aspects of growth. That is, these three different growth curve parameters may have, to some extent, unique genetic underpinnings.

In a recent association study, Towne et al.[39] found evidence of the effects of a functional polymorphism in the β-subunit of the luteinizing hormone gene (LH-β) on stature during childhood. A total of 736 individuals, from 137 nuclear and extended families, measured a total of 13,300 times between 2 and 18 years old, were genotyped for the LH-β polymorphism. Individuals with the less common LH-β allele were found to be shorter than those homozygous for the common LH-β allele at all childhood ages.

With regard to the genetics of development, Towne et al.[40] used a multivariate variance components method incorporating parametric correlation functions to model the heritability of skeletal maturity in children from 3 to 15 years old and the genetic and environmental correlations between skeletal maturity assessed across this age range. A total of 6893 annual skeletal age assessments, made from hand-wrist radiographs taken of 807 children from 192 nuclear and extended families, were simultaneously analyzed. The best-fitting model had 65 parameters and allowed for an exponential decay in genetic and environmental correlations as a function of chronological age differences. From this model, the h^2 estimates of skeletal age

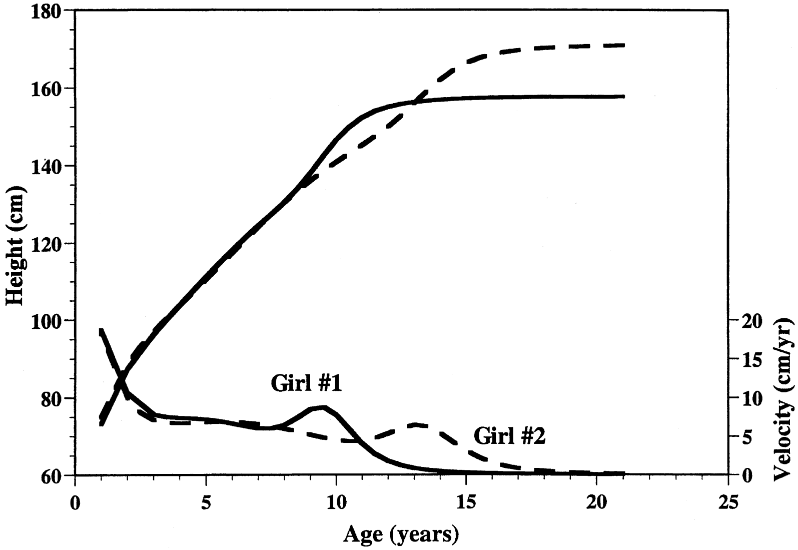

FIGURE 6-3 Height distance and velocity curves for two girls with different growth patterns between 12 months and 20 years old.

at each chronological age were 3 = 0.71, 4 = 0.73, 5 = 0.77, 6 = 0.93, 7 = 0.78, 8 = 0.77, 9 = 0.73, 10 = 0.63, 11 = 0.45, 12 = 0.39, 13 = 0.34, 14 = 0.23, and 15 = 0.11. The genetic correlation matrix showed a pattern of decreasing correlations between skeletal age at different chronological ages as age differences increased (e.g., ρ_G between skeletal age at 3 years old and skeletal age at 4 years old was 0.96, but between skeletal age at 3 years old and skeletal age at 15 years old, ρ_G was 0.56). The random environmental correlation matrix showed an even more pronounced pattern of decreasing correlations between skeletal age at different chronological ages as age differences increased (e.g., ρ_E between skeletal age at 3 years old and skeletal age at 4 years old was 0.77, but ρ_E between skeletal age at 3 years old and skeletal age at 15 years old was only 0.12). These results show a high heritability of skeletal age through early puberty and suggest that skeletal maturation at different stages of development is influenced by different sets of genes and environmental factors.

Jiri Growth Study

The goal of the Jiri Growth Study is to elucidate the roles of genetic and environmental factors influencing processes of childhood growth and development. This is being accomplished by establishing a longitudinal study of the growth and development of a large cohort of related children living in rural Nepal, where gastrointestinal parasitic diseases (helminthic and protozoan infections in particular) are endemic. Initiated in 1998 by one of the authors (B.T.), the Jiri Growth Study is an infant compared to the 73-year-old Fels Longitudinal Study. But, by virtue of its extended pedigree study design and the use of modern statistical genetic methods, it will not take long to mature into a genetic epidemiological study of growth and development.

The Jiri Growth Study is an offshoot of the Jiri Helminth Project. The Jiri Helminth Project began in 1995 as a collaborative effort of U.S. and Nepali investigators, with primary grant funding from the U.S. National Institutes of Health to Sarah Williams-Blangero and John Blangero in the Department of Genetics at the Southwest Foundation for Biomedical Research. The goal of the Jiri Helminth Project is to examine both genetic and environmental factors that predispose individuals to helminthic infection.

Roundworm, hookworm, and whipworm are major health concerns in both tropical and temperate areas of the world. Worldwide, approximately one out of every four persons is infected by at least one of these three helminths. They are major causes of morbidity in developing nations and significant causes of mortality in areas with limited health care. Increasing urbanization in many areas of the developing world, usually without adequate infrastructure development (e.g., water and sanitation systems), has resulted in increasing rates of intestinal parasitic infections.

There has been increasing evidence over the last 20 years that susceptibility or predisposition to helminthic infection has a genetic component, with several studies finding familial aggregation of roundworm and whipworm infections. None of these studies, however, were conducted using data from large numbers of relatives and modern genetic epidemiological approaches. The Jirel ethnic group in the Jiri region of eastern Nepal is an ideal study population in which to examine the genetic epidemiology of helminthic infection. The Jirel population today numbers approximately 4000 individuals, who live in nine villages. The Jirels have been the focus of extensive anthropologic, population genetic, and genetic epidemiologic studies over the last 15 years. Over this time the complete genealogy of the Jirel population has been compiled. Almost all Jirels trace their ancestry back approximately 150 years to a population of some 200 individuals. Most Jirels today are members of one very large extended pedigree of approximately 3500 individuals.

The tremendous power that this population structure provides for genetic epidemiologic research is evidenced in the tens of thousands of pairwise kin relationships that exist among the some 2000 Jirels participating in the Jiri Helminth Project. For example, Williams-Blangero et al.[41] recently reported h^2 estimates between 0.30 and 0.50 for different quantifications of roundworm burden (i.e., egg counts and worm counts). Similar heritabilities for hookworm and whipworm infection have been estimated in preliminary analyses (Williams-Blangero, personal communication). These results demonstrate a highly significant genetic basis to susceptibility to helminthic infection in the Jirel population.

Given the negative impact that helminthic infections have on growth and development, it is reasonable to hypothesize that genes predisposing for susceptibility to helminthic infection also negatively influence processes of growth and development. In an initial analysis of height and roundworm infection status data from 432 Jirel children, Towne, Blangero, and Williams-Blangero[42] found a high h^2 of 0.91 for height and negative associations of height with roundworm infection status, with the effect being more pronounced in males. For example, on average, a 12-year-old boy infected with roundworms would be 2.2 cm shorter than an uninfected 12-year-old boy, while an infected 12-year-old girl would be only 0.5 cm shorter than an uninfected 12-year-old girl.

Ultimately, some 1000 Jirel children will be examined on a regular basis as part of the Jiri Growth Study. In addition to annual quantitative determinations of helminthic and protozoan infections, a comprehensive battery of anthropometrics, body composition measures, developmental indicators, and blood biochemistries will be collected from each child. Extensive sociocultural survey data also will be collected to examine associations between growth and development and features of household environment. The Jiri Growth Study offers unique opportunities to quantify genetic and environmental factors influencing growth and development over the course of childhood and to explicitly examine genotype-by-environment interaction effects on human growth and development.

CONCLUSION

For over a century, there has been scientific interest in the genetic underpinnings of growth and development. But, as with any area of scientific inquiry, to one degree or another, all studies of the genetics of growth and development have been limited by the methods and technologies available to them at the time. For that reason, most of the literature is limited to heritability estimates of measures of growth and development gathered from first-degree relatives. The opportunities exist today, however, for much more sophisticated studies of both genetic and environmental factors that influence the processes of growth and development.

One problem, though, is that modern genetic epidemiological studies of growth and development can be expensive undertakings. Such studies are readily justified, however, on the very practical and applied grounds that growth and development of children can have health consequences later in life. Indeed, much of the current research emphasis in the Fels Longitudinal Study pertains to studies of the relationships between age-related changes in body composition (including those that occur during childhood) and the development and progression of cardiovascular disease (CVD) risk factors in later life, an area of active research today. A current Fels Longitudinal Study project, for example, is aimed at evaluating the role of birth weight in predisposing to adult CVD, taking into account the significant heritable components of both birth weight and various measures of adult CVD risk. Demerath et al.[43] recently found that birth weight was negatively associated with fasting insulin concentration in adulthood after adjusting for BMI and age, but after taking into account the significant heritability of insulin concentration, birth weight only accounted for 1–2% of the remaining phenotypic variance of fasting insulin concentration. Another current Fels Longitudinal Study project is examining changes in serum lipids during growth and development. Although lipid and lipoprotein levels track from childhood to adulthood, Czerwinski et al.[44] found higher heritabilities of lipids and lipoproteins after puberty than before, suggesting that the genetic control of lipid and lipoprotein levels may be influenced by maturational factors.

We hope this chapter has demonstrated that the processes of growth and development are to a large extent controlled by genes; therefore, the first task in establishing a genetic epidemiology of growth discussed in the Introduction: "characterizing the magnitude of genetic influences on growth and development phenotypes" has been essentially completed. Auxological genetics is now poised to move beyond this critical but basic assertion to a thorough understanding of the sources of genetic control over growth during prenatal and postnatal life. This will involve examining how those genetic influences operate over time, identifying and localizing specific genetic polymorphisms that contribute to variation in growth and development, and elucidating how genetic and environmental factors interact during growth and development. Given the advances in statistical and molecular genetics made over the last 20 years and the renewed interest in childhood growth due to its potential relationship with diseases of adulthood, these goals may now be achieved.

GLOSSARY

Allele: A variant of the DNA sequence at a particular locus. Typically, individuals possess two allelic variants at each locus, derived from the maternal and paternal chromosomes, respectively. The two alleles may be identical or different, making the individual homozygous or heterozygous, respectively, at that locus.

Assortative mating: Selection of a mate based on phenotypic characteristics. Positive assortative mating occurs when selection is based on a shared character. Negative assortative mating occurs when selection is based on an unshared character.

Complex trait or phenotype: Any phenotype whose expression is influenced by multiple genes, or by one or more genes and one or more environmental factors. Complex traits can be quantitative or discrete.

Epistasis: Interactions between alleles at different loci. Also known as gene × gene interaction.

Gene: A segment of DNA that codes for a specific protein or enzyme.

Genotype: The group of genes making up an organism. The genotype at a particular locus consists of the two alleles present at that locus.

Heritability: A measure that expresses the extent to which phenotypes are determined by genes transmitted from parents to their offspring. *Heritability* (in the narrow sense) is defined as the proportion of the total phenotypic variance attributable to the additive effects of genes.

Identity by descent (IBD): Identical alleles at the same locus found in two related individuals that are identical because they originated from a common ancestor.

Identity by state (IBS): Identical alleles found within two individuals. If the two individuals are related, the two alleles may also be identical by descent if they are replicates of the same ancestral allele from a previous generation.

Kinship coefficient: The probability that two genes from two individuals for a given locus are identical by descent. A general measure of relatedness.

Linkage analysis: A method of analysis used to localize the position of genes on a chromosome.

Linkage disequilibrium: Nonrandom association within a population of alleles at two or more linked loci. Linkage disequilibrium decays with increasing genetic (recombination) distance between loci.

Locus: The position of a gene on a chromosome.

Monogenic: A trait is monogenic if it is influenced primarily or entirely by only one genetic locus.

Mutation: Specific sequence variants in the nucleotide sequence of a gene. These variants may or may not be inherited.

Oligogenic: A trait is oligogenic if it is influenced by a few loci of significant, individually detectable effects.

Phenotype: The observable characteristics of an organism or a specific trait produced by the genotype in conjunction with the environment.

Polygenic: A phenotype is polygenic if it is influenced by many genes of relatively small individual effects, such that the influence of any single locus is very difficult or impossible to detect on its own.

Polymorphism: The joint occurrence in a population of two or more genetically determined alternative phenotypes, each occurring at an appreciable frequency (arbitrarily, 1% or higher). A polymorphism may be defined at either the protein level (e.g., Rh+ and Rh– red blood cell groups) or at the DNA level (alternative alleles at a locus).

Quantitative trait locus: Any locus that influences variation in a complex phenotype.

Recombination (crossover): The exchange of segments of homologous chromosomes following chromosomal duplication and synapse formation during meiosis. Recombination is responsible for the production of offspring with combinations of alleles at linked loci that differ from those possessed by the two parents.

SUGGESTED READING

Hartl DL. A Primer of Population Genetics. Sunderland, MA: Sinauer Associates, 1999.

Hartl DL, Clark AG. Principles of Population Genetics. Sunderland, MA: Sinauer Associates, 1997.

Khoury MJ, Cohen BH, Beaty TH. Fundamentals of Genetic Epidemiology. Oxford: Oxford University Press, 1993.

Lynch M, Walsh B. Genetic Analysis of Quantitative Traits. Sunderland, MA: Sinauer Associates, 1997.

Ott J. Analysis of Human Genetic Linkage. Baltimore: Johns Hopkins University Press, 1999.

Terwilliger JD, Ott J. Handbook of Human Genetic Linkage. Baltimore: Johns Hopkins University Press, 1994.

Weiss KM. Genetic Variation and Human Disease: Principles and Evolutionary Approaches. New York: Cambridge University Press, 1993.

INTERNET RESOURCES

Site	Site Address
Center for Medical Genetics (Marshfield, WI)	http://www.marshmed.org/genetics/
Cooperative Human Linkage Center	http://www.chlc.org/
GENATLAS QUERY	http://bisance.citi2.fr/GENATLAS/

Site	Site Address
Genetics-related resources	http://linkage.rockefeller.edu/outside/list.html
OMIM Home Page—Online Mendelian Inheritance	http://www3.ncbi.nlm.nih.gov/Omim/
The Genome Database	http://gdbwww.gdb.org/
The Human Genetic Analysis Resource	http://darwin.cwru.edu/
Genetic linkage analysis	http://linkage.rockefeller.edu/
National Human Genome Research Institute (NHGRI)	http://www.nhgri.nih.gov/
Genome Research	http://www.er.doe.gov/production/ober/hugtop.html
National Center for Biotechnology Information	http://www.ncbi.nlm.nih.gov/
Human obesity gene maps	http://www.obesite.chaire.ulaval.ca/genes.html

REFERENCES

1. Neel J, Schull W. Human Heredity. Chicago; London: University of Chicago Press, 1954.
2. Falconer DS, Mackay TFC. Introduction to Quantitative Genetics, 4th ed. Harlow, UK: Longman, 1996.
3. Lynch M, Walsh B. Genetic Analysis of Quantitative Traits. Sunderland, MA: Sinauer Associates, 1997.
4. Fisher RA. The correlation between relatives on the supposition of Mendelian inheritance. Trans Royal Soc Edinburgh. 1918;52:399–433.
5. Eveleth PB, Tanner JM. Worldwide Variation in Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1990.
6. Martorell R, Mendoza F, Castillo R. Poverty and stature in children. In: Waterlow JC (ed). Linear Growth Retardation in Less Developed Countries. New York: Raven Press, 1988:57–73.
7. Mueller WH. Genetic and environmental influences on fetal growth. In: Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998:133–136.
8. Penrose L. Some recent trends in human genetics. Caryologia. 1954;6(Suppl):521.
9. Wilson R. Concordance in physical growth for monozygotic and dizygotic twins. Ann Hum Biol. 1976;3:1–10.
10. Pearson K, Lee A. On the laws of inheritance in man. I. Inheritance of physical characteristics. Biometr. 1903;2:356–462.
11. Mueller WH. Parent-child correlations for stature and weight among school-aged children: A review of 24 studies. Hum Biol. 1976;48:379–397.
12. Garn SM, Rohmann CG. Interaction of nutrition and genetics in the timing of growth and development. Ped Clin N Amer. 1966;13:353–379.
13. Welon Z, Bielicki T. Further investigations of parent-child similarity in stature as assessed from longitudinal data. Hum Biol. 1971;43:517–525.
14. Tanner J, Goldstein H, Whitehouse R. Standards for children's height at ages 2–9 years allowing for height of the parents. Arch Dis Child. 1970;45:755–762.
15. Furusho T. On the manifestations of the genotypes responsible for stature. Hum Biol. 1968;40:437–455.
16. Beunen G, Maes H, Vlietinck R, et al. Univariate and multivariate genetic analysis of subcutaneous fatness and fat distribution in early adolescence. Behav Gen. 1998;28:279–288.

17. Garn S, Lewis A, Polacheck D. Sibling similarities in dental development. J Dent Res. 1960;39:170–175.
18. Hewitt D. Some familial correlations in height, weight and skeletal maturity. Ann Hum Genet. 1957;22:26–35.
19. Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.
20. Boas F. Studies in growth. Hum Biol. 1932;4:307–350.
21. Damon A, Damon S, Pred R, Valadian I. Age at menarche of mothers and daughters with a note on accuracy of recall. Hum Biol. 1969;41:160–175.
22. Zacharias L, Rand W, Wurtman R. A prospective study of sexual development and growth in American girls: The statistics of menarche. Obstet Gynec Surv. 1976;31:325–337.
23. Meyer J, Eaves L, Heath A, Martin N. Estimating genetic influences on the age-at-menarche: A survival analysis approach. Amer J Med Genet. 1991;39:148–154.
24. Malina R, Ryan R, Bonci C. Age at menarche in athletes and their mothers and sisters. Ann Hum Biol. 1994;21:417–422.
25. Brooks-Gunn J, Warren MP. Mother-daughter differences in menarcheal age in adolescent girls attending national dance company schools and non-dancers. Ann Hum Biol. 1988;15:35–44.
26. Loesch D, Huggins R, Rogucka E, Hoang N, Hopper J. Genetic correlates of menarcheal age: A multivariate twin study. Ann Hum Biol. 1995;22:479–490.
27. Sontag L. The Fels Research Institute for the Study of Human Development. Yellow Springs, OH: Antioch College Press, 1946.
28. Sontag L, Nelson V. A study of identical triplets. Part I. Comparison of the physical and mental traits of a set of monozygotic dichorionic triplets. J Hered. 1933;24:473–480.
29. Sontag L, Comstock G. Striae in bones of a set of monozygotic triplets. Amer J Dis Child. 1938;56:301–308.
30. Sontag L, Reynolds E. Ossification sequences in identical triplets. A longitudinal study of resemblances and differences in the ossification patterns of a set of monozygotic triplets. J Hered. 1944;35:57–64.
31. Reynolds E, Schoen G. Growth patterns of identical triplets from 8 through 18 years. Child Devel. 1947;18:130–151.
32. Reynolds E. Degree of kinship and pattern of ossification. Amer J Phys Anthropol. 1943;1:405–416.
33. Garn S, Lewis A, Kerewsky R. Third molar agenesis and size reduction of the remaining teeth. Nature. 1963;200:488–489.
34. Garn S, Lewis A, Walenga A. The genetic basis of the crown-size profile pattern. J Dent Res. 1968;47:1190.
35. Garn S, Lewis A, Kerewsky R, Dahlberg A. Genetic independence of Carabelli's trait from tooth size or crown morphology. Arch Oral Biol. 1966;11:745–747.
36. Towne B, Guo S, Roche A, Siervogel R. Genetic analysis of patterns of growth in infant recumbent length. Hum Biol. 1993;65:977–989.
37. Towne B, Parks JS, Guo S, Siervogel RM. Quantitative genetic analysis of associations between pubertal growth spurt parameters. Amer J Hum Genet. 1995;57(Suppl):A173.
38. AUXAL. Auxological Analysis of Longitudinal Measurements of Human Stature program. Version: DOS Auxal 2. Chicago: Scientific Software International, 1994.
39. Towne B, Parks JS, Brown MR, Siervogel RM, Blangero J. Effect of a luteinizing hormone β-subunit polymorphism on growth in stature. Acta Medica Auxol (abstract). 2000;32(1):43.
40. Towne B, Siervogel RM, Parks JS, Brown MR, Roche AF, Blangero J. Genetic regulation of skeletal maturation from 3 to 15 years. Amer J Hum Genet. 1999;S65:A401.
41. Williams-Blangero S, Subedi J, Upadhayay R, et al. Genetic analysis of susceptibility to infection with *Ascaris lumbricoides*. Amer J Trop Med Hyg. 1999;60:921–926.
42. Towne B, Blangero J, Williams-Blangero S. Genetic and environmental influences on the growth status of Nepali children. Amer J Hum Biol. 2000;12(2):278.
43. Demerath E, Towne B, Czerwinski S, Siervogel R. Covariate effect of birth weight in a genetic analysis of fasting insulin and glucose concentrations in adulthood. Diabetes. 2000;49(Suppl 1):A183.

44. Czerwinski SA, Towne B, Guo S, Chumlea WC, Roche AF, Siervogel RM. Genetic and environmental influences on lipid and lipoprotein levels in pre- and post-pubertal children. Amer J Hum Biol. 2000;12:289.
45. Clausson B, Lichtenstein P, Cnattinigius S. Genetic influence on birthweight and gestational length determined by studies in offspring of twins. Brit J Genet. 2000;107:375–381.
46. Nance W, Kramer A, Corey L, Winter P, Eaves L. A causal analysis of birth weight in the offspring of monozygotic twins. Amer J Hum Genet. 1983;35:1211–1223.
47. Morton N. The inheritance of human birth weight. Ann Hum Genet. 1955;20:125.
48. Susanne C. Heritability of anthropological characters. Hum Biol. 1977;49:573–580.
49. Solomon P, Thompson E, Rissanen A. The inheritance of height in a Finnish population. Ann Hum Biol. 1983;10:247–256.
50. Malina R, Mueller W, Holman J. Parent-child correlations and heritability of stature in Philadelphia black and white children 6 to 12 years of age. Hum Biol. 1976;48:475–486.
51. Garn S, Bailey S, Cole P. Similarities between parents and their adopted children. Amer J Phys Anthropol. 1976;45:539–543.
52. Fischbein S. Intra-pair similarity in physical growth of monozygotic and of dizygotic twins during puberty. Ann Hum Biol. 1977;4:417–430.
53. Fischbein S, Nordqvist T. Profile comparisons of physical growth for monozygotic and dizygotic twin pairs. Ann Hum Biol. 1978;5:321–328.
54. Byard P, Guo S, Roche A. Family resemblance for Preece-Baines growth curve parameters in the Fels Longitudinal Study. Amer J Hum Biol. 1993;5:151–157.
55. Vandenberg S, Falkner F. Hereditary factors in human growth. Hum Biol. 1965;37:357–365.
56. Hauspie RC, Bergman P, Bielicki T, Susanne C. Genetic variance in the pattern of the growth curve for height: A longitudinal analysis of male twins. Ann Hum Biol. 1994;21:347–362.
57. Roberts D, Billewicz W, McGregor I. Heritability of stature in a West African population. Ann Hum Genet. 1978;42:15–24.
58. Mueller W, Titcomb M. Genetic and environmental determinants of growth of school-aged children in a rural Colombian population. Ann Hum Biol. 1977;4:1–15.
59. Devi M, Reddi G. Heritability of body measurements among the Jalari population of Cisakhapatnam. Ann Hum Biol. 1983;10:483–485.
60. Kaur D, Singh R. Parent-adult offspring correlations and heritability of body measurements in a rural Indian population. Ann Hum Biol. 1981;8:333–339.
61. Sharma K, Byard P, Russell J, Rao D. A family study of anthropometric traits in a Punjabi community: I. Introduction and familial correlations. Amer J Phys Anthropol. 1984;63:389–395.
62. Ikoma E, Kanda S, Nakata S, Wada Y, Yamazaki K. Quantitative genetic analysis of bi-iliac breadth. Amer J Phys Anthropol. 1988;77:295–301.
63. Orley J. Analysis of menarche and gynecological welfare of Budapest school girls. In: Eiben O (ed). Growth and Development: Physique. Budapest: Adademiai Kiado, 1977:191–194.

7

NUTRITION AND GROWTH

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INTRODUCTION

It is self-evident that nutrition is essential for growth. Growth is, in this context, an increase in size and mass of the constituents of the body. The only way this can be achieved is from the environment. *Nutrition* is defined as the process whereby living organisms take in and transform extraneous solid and liquid substances necessary for maintenance of life, growth, the normal functioning of organs, and the production of energy.

The constituents of our bodies, the structure and chemical composition of our cells, tissues, and organs, are remarkably similar all over the world. Indeed, the similarity extends to much of the animal kingdom. The lean body mass typically consists of 72% water, 21% protein, 7% minerals, and less than 1% of carbohydrate and other nutrients. Yet, we have available and select or tolerate a very wide range of foodstuffs and diet types. This leads to the first truism of nutrition and growth, that a wide range of diet types is capable of satisfying nutritional needs and promoting optimal growth. What determines the particular diet we consume involves a myriad of factors. For much of human evolution and for some groups today, the physical environment and climate determined what could be procured or cultivated. However, technology and the economic power to develop and exploit it allow us to inhabit the polar regions, the ocean depths, and space, environments that do not naturally support food production. Economic and political systems are the major factors influencing food choice and whether food intake is sufficient to allow growth potential to be achieved.

This chapter has the following aims:

- To illustrate the importance of an understanding of methodology in a consideration of nutrition and growth.
- To recognize that, although growth is highly nutrition sensitive, for much of the growth period, the nutritional requirements for growth per se are only a small proportion of the total requirement.
- To demonstrate that growth perturbation is usually of multifactorial origin.
- To understand the need to assess the contribution of nutrition to growth perturbation in the total environment in order to identify the appropriate remedial actions.

NUTRITION FOR STUDENTS OF GROWTH

Importance of Methodology

Students of growth need an understanding of some of the basic principles of nutrition if they are to understand and critically evaluate issues in nutrition and growth. As in other fields, it is important to be able to assess the strengths and weaknesses of evidence. There are regular surveys of food intake in many countries and frequent research reports on dietary intake and nutritional status. However, a number of issues must be considered. The apparently simple task of collecting accurate, representative data of the food intake of people going about their everyday way of life is notoriously difficult, and that difficulty should not be underestimated. Much of the information may have been collected by pragmatic but not necessarily the most accurate techniques.

Similarly, it is not difficult for the student to find in textbooks, on websites, or in government and research reports accounts of what are the nutritional needs of the various members of the population. However, the bases to these figures and their correct use is not straightforward. If the reader is to be informed in order to make critical observation, thought, and decisions on nutrition and growth, it is important that these intricacies are known and remembered.

Measurement of Food and Nutrient and Energy Intake

The measurement of habitual food intake is an example of Heisenberg's uncertainty principle: The harder you try to measure it, the more likely you are to affect what you are trying to measure. Nutritionists are able to perform accurate, to less than 1% of the real value, measurements of energy and nutrient intake. The participants are housed in nutrition units and provided their meals. Duplicate meals and snacks are weighed and analyzed by good physical and chemical analytical methods. (It is true that you can never analyze what someone has eaten because, if they have eaten it, you cannot analyze it, and if you have analyzed it, they cannot eat it.) The problems arise when we become interested in habitual food intake in people leading their everyday lives. It is difficult or inconvenient to weigh the food consumed in many circumstances. The inconvenience of weighing may influence the foods people eat or the number of meals and snacks they consume. A further problem in population studies is the need for statistical considerations of adequate numbers. There may be logistical and financial considerations and constraints, and these may influence the choice of method. Most dietary surveys adopt the simple methods of questionnaire, interview, or other subjective assessment to assess food intake and translate these to nutrients and energy intakes using tables of food composition. There are problems with the use of food tables, too. The data on composition in food tables may not match those of the food consumed.

There is, thus, a trade-off between ease of use and acceptability to participants and accuracy. In some cases, simple techniques may be appropriate. Some epidemiological investigations may require individuals to be assigned only to a correct tertile of intake: high, medium or low. However, it is crucial when reading the literature to be able to decide if the nutritional methods used are fit for purpose. The literature abounds with studies purporting to show that children are inadequately nourished based on ignorance of either the limitations of the intake data or, more usually, the nature of figures for recommended intake.

Dietary Requirements and Recommended Intake

Determination of Dietary Requirements and Recommended Intakes

We have nutritional needs, because being in a state of turnover, we have loss of body constituents and because at certain times of the life span, such as growth and pregnancy, we have a net gain of tissue. An individual's dietary requirements can be ascertained by measuring these losses and gains. Under most circumstances, such determinations are not practical and our judgments have to be based on the available experimental and other evidence from other individuals. However, individuals vary in their dietary requirements, even after taking into account age, sex, and size. Therefore, we can make statements about only the probability of what an individual's requirement for a particular nutrient might be or the probability that a particular intake will be adequate or inadequate. This has led nutritionists to develop a series of values, including their best estimates of the average requirement for a given group of healthy individuals given the circumstances under which they live. The series usually includes a high level, thought to represent the needs of most of the group, and a lower level, below which most individuals would have an inadequate intake. In some cases, a high level, above which problems of toxicity may be expected, is also identified.

Evidence on nutrient requirements has been gained in a variety of ways. Toward the end of the nineteenth century, medical scientists investigated the types and amounts of foods associated with good health or that would lead to the reversal of signs of nutrient deficiencies. They labored under the difficulty of the hegemony of the germ theory of disease following the work of Pasteur and Koch. Around the turn of the twentieth century, physiologists conducted animal and human experiments on artificial and deficient diets with nutrients fed at a variety of levels to ascertain needs. These were essentially balance experiments, with allowances for growth and production. A variation has been the factorial approach, which measures all the avenues of losses from the body—urine, feces, sweat, secretions, and other emanations—to calculate the total losses. A further approach has been to determine the level of intake associated with high or maximum levels of the nutrient in the body. This invariably produces higher estimates of requirements than the other approaches.

A problem with the balance approach is that the body can be in balance but in a state of over- or undernutrition that may be hazardous to health owing to changes or adaptations that occur to varying planes of nutrient intakes. Two difficulties emerge. First is the identification of the range of intakes where balance is not associated with risk. The second is whether recommended intakes should be set to maintain the status quo or at levels that are normative and lead to balance at the lower risk range. The problem is most acute for energy. We may calculate an allowance for children to take up aerobic exercise to promote cardiorespiratory fitness and body composition. However, if they are not active, the recommendation would be a prescription for weight gain and obesity. As usual, a decision has to be made according to the context. The FAO/WHO/UNU[1] recommendations for energy intended to be applicable to individuals all over the world include components for desirable but discretionary activities; that is, they are normative. The United Kingdom recommendations do not.[2] They are values to maintain the status quo.

Nutrient Requirements and Recommended Intake

Many countries have drawn up their own recommendations for nutrient intake. They may have been drawn up and published in slightly different ways, but there is some communality in their types.

The *estimated average requirement* (EAR) is what it says it is, except in the United States, where it is actually a median not an average or mean. It refers to a particular group according to age, sex, possibly body size and composition, and in some cases, lifestyle. It is used as one factor for assessing the adequacy of intake of an individual or groups and for planning intake of groups. Approximately half the members of the group will need more and half less than the EAR.

The upper level, at or above which daily intake of a nutrient will meet the needs of most individuals in the specified group, is usually set at the average or median requirement plus two standard deviations (SD). Where distributions of requirements are know to be skewed, the 97.5 percentile may be used. This level is called *reference nutrient intake* (RNI) in the United Kingdom and *recommended dietary allowance* (RDA) in the United States. It is intended as a goal for the intake of healthy individuals. It is not intended to be used to assess individual or group intake, as most of the population require, and can stay healthy, on an intake lower than these.

One of the commonest mistakes or misleading actions in nutrition is to assume that, if an individual or group consumes less than the RNI or RDA, the intake is inadequate. There is no shortage of examples of this occurrence. The U.S. National Institute of Child Health and Human Development website has a table titled "Calcium: Who Gets Enough," showing that approximately 50% of children under 12 years old were getting the 1989 RDA.[3] The implication is that the other 50% were not getting enough. But 97% could be consuming less than the RDA but be getting enough! All that can be said is that, as the intake becomes a lower proportion of the RDA, the *risk* of dietary nutrient inadequacy increases. Students of growth should have less of a problem with this point, as they are accustomed not to expect every child to be at the 97.5th percentile for height. Similarly, not every child's nutrient intake needs to be at the 97.5th percentile of requirements. It may be prudent to be at that level, but prudence should not be confused with proof of nutrient inadequacy.

A further point is that, as recommendations vary among countries, given intakes can represent much greater percentages of the reference intake in some countries than others. Such discrepancies do not reflect inherent biological differences but the different approaches and conclusions of the national advisory committees. Table 7-1 compares the United Kingdom's RNI and the United States' RDA for selected nutrients for children 1–10 years old. In the main, the RDAs are higher than RNIs. The United States' RDAs are some of the highest in the world, surpassed only by those from Germany.

The certainty about statements of dietary inadequacy would be increased if a lower level were used. The United Kingdom has a *lower reference nutrient intake*

TABLE 7-1 The United Kingdom (UK) Reference Nutrient Intakes and the United States (USA) Acceptable Intakes of Selected Nutrients for Children 1–10 Years Old

Age Group	1–3 Years		4–6 Years		7–10 Years	
Country	UK	USA	UK	USA	UK	USA
Protein, g/day	15.4	16	19.7	24	28.3	28
Energy, kcal/day		1300		1800		2000
Boys	1230		1715		1970	
Girls	1165		1545		1740	
Calcium, mg/day	350	800	450	800	550	800
Iron, mg/day	6.9	10	6.1	10	8.7	10
Zinc, mg/day	5.0	10	6.5	10	7.0	10
Vitamin C, mg/day	30	40	30	45	30	45
Vitamin D, µg/day	7	10	—	10	—	10

See Bibliography for references.

(LRNI), the level below which intakes are likely to be inadequate for the large majority of the specified group. It is taken as the mean –2 SD.

A fourth type of value is published when there is insufficient information to determine the other types. In the United Kingdom, *safe intakes* are specified when there is not enough information to estimate RNI, EAR, or LRNI. This is the amount that is sufficient for almost everyone in a specified group but not so large as to cause undesirable effects. In the United States, when insufficient evidence exists to determine EAR, an *adequate intake* (AI) is specified. This is intended to cover the needs of most individuals in a specified group but the percentage cannot be stated with certainty. Therefore, these are at a level comparable to RNI and RDA but have even more uncertainty about them. In the United States, AI rather than EAR or RDA has been proposed for all nutrients for infants up to 1 year old and for calcium and vitamin D for all life stages.

Finally, the maximum level that is unlikely to pose risks to health in almost all individuals in the specified group is called the *tolerable upper intake level* (UL) in the United States. This does not mean that intakes above RNI or RDA have known nutritional benefits. Also, for many nutrients, there is insufficient data on the levels at which adverse effects occur.

Energy Requirements

According to FAO/WHO/UNU[1]:

> *The energy requirement of an individual is the level of energy intake from food that will balance energy expenditure when the individual has a body size and composition and level of physical activity, consistent with long-term good health; and that will allow for the maintenance of economically necessary and socially desirable physical activity. In children and pregnant and lactating women the energy requirement includes the energy needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.*

Not every nutritionist feels comfortable with this definition, because of the problems in establishing what is a state of long-term good health and the possible subjectivity of socially desirable physical activity. However, a more immediate problem is the need to know the energy expenditure. This can be approached at a variety of levels. An estimate can be made knowing the age, sex and weight of the child and assuming a type of lifestyle—inactive, moderately active, and so forth. At the other end of the range of approaches is the measurement using stable isotopic doubly labeled water. This has the disadvantage of being expensive and lacking information on the components of the energy expenditure. Somewhere in between is the factorial approach of recording the time and duration of activity and applying energy costs either measured or taken from the literature to these to calculate energy expenditure.[4] It can be seen that there are considerable differences in the certainty of estimates of energy expenditure from these different approaches and, hence, in the estimates of energy requirements.

Protein Requirements

> *The protein requirement of an individual is defined as the lowest level of dietary protein intake that will balance losses of nitrogen in persons maintaining energy balance at modest levels of physical activity. In children and pregnant or lactating women, the protein requirement is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.*[1]

Protein-Energy Ratios

The adequacy of a protein intake is influenced by the adequacy of the energy intake. When energy intake is inadequate, there may be a net negative nitrogen balance that reduces the adequacy of the protein intake. Thus, information on energy and protein intake need to be considered together. One way of doing this is the protein-energy ratio (PE ratio: protein energy/total energy). When the diet exceeds the safe PE ratio, then any protein nutrition problems will result from inadequate amounts of food rather than low protein content. Most regular diets have PE ratios between 10 and 15%. Human breast milk has a PE ratio of about 7% and is adequate for the rapid growth in the first months of life. In the absence of other detailed information, this figure can be applied to other stages of growth. An allowance has to be made for the efficiency of utilization of the protein, which in most cases is less than that of breast milk.

Micronutrient Requirements

These usually have been assessed by balance techniques. An alternative approach common in North America is to identify the dietary intake associated with the highest levels in the body. These different approaches explain much of the differences in the United Kingdom's RNI and the United States' AI described earlier.

Dietary Goals and Guidelines

Dietary goals and guidelines differ from dietary recommended intakes and dietary reference values. Dietary guidelines provide advice on food selection that will help meet the RDA or RNI and help reduce the risk of disease, particularly chronic disease. They are thus meant to ensure adequate intake to prevent deficiency states and prevent the inappropriate macronutrient intakes associated with many of the chronic degenerative diseases of affluent societies. The goals set what is to be achieved to reduce the incidence of these diseases in terms that are understood by the professionals; that is, reduce intake of nutrient x to y g per day. The guidelines indicate to the public how the goals are to be achieved. They refer to foods and diets as opposed to nutrients. As most of us base our diet on foods rather than nutrients, they are much more relevant to the population.

The most well-known dietary guideline is to eat a variety of foods. This is usually portrayed as a food block, plate, or pyramid of 4–5 food groups that recommends the kinds and amounts of foods to be eaten each day. The United States' food guide pyramid indicates fats, oils, and sweets are to be used sparingly, but there can be 6–11 servings of bread, cereal, rice, and pasta. The United Kingdom's national food guide uses a picture of a plate with less prescription on servings but essentially the same advice.

Dietary guidelines are regarded as applicable to the whole population. Australia and New Zealand produced guidelines specifically for children of different ages, which allow for fuller consideration of types of infant feeding and the nutritional problems of adolescents. The United States has a food guide pyramid for young children, meant to be accessible to 2–6 year olds.[5]

Values of recommended intakes and dietary goals and guidelines have another important use in addition to assessing or planning diets. This is in the information given on and claims made for food products, particularly on labels. Food manufacturers are interested in dietary recommended values and legislation about food composition and claims. They are important members of the committees that draw up guidelines, often with interests separate to those of nutritionists and clinicians. This may not be counterproductive, as differing views may lead to better evidence on requirements and recommendations in the long term.

Assessment of Nutritional Status

The assessment of the nutritional status of an individual or group involves the collection of information: on diet, biochemical indices, anthropometry, clinical signs, and morbidity and mortality statistics. The value and place of this disparate group of measurements can best be understood by considering the process of becoming malnourished. Figure 7-1 shows the process of moving from a state of good nutrition to malnutrition and eventually death and shows the place of each type of measurement. The aim should be to correctly describe an individual or group as well nourished, at risk, to be monitored further, or in need of remedial action.

The directionality of the process may need to be established by serial measurements, as for example, poor scores on biochemical, anthropometric, and clinical data may persist for sometime after the diet has improved. Good dietary assessment is difficult, time consuming, and expensive; and its interpretation is rarely clear-cut, given the nature of knowledge of nutritional requirements, and this is often omitted. However, it can be crucial in establishing the true pathogenesis, as many of the other signs are not specific to nutrition but can also arise from other environmental causes such as disease. A wide-ranging ecological assessment may be the only way to ensure that the true causes of low nutritional status are identified and the appropriate remedial action is taken.

The emphasis in assessment is to obtain early warning signs of malnutrition, and the biochemical indices play an important role here. Simple dietary iron deficiency will result in iron-deficiency anemia (low levels of hemoglobin, with microcytic and hypochromic erythrocytes) if left untreated. Before hemoglobin levels fall, body stores diminish. This is described as iron deficiency without anemia. In

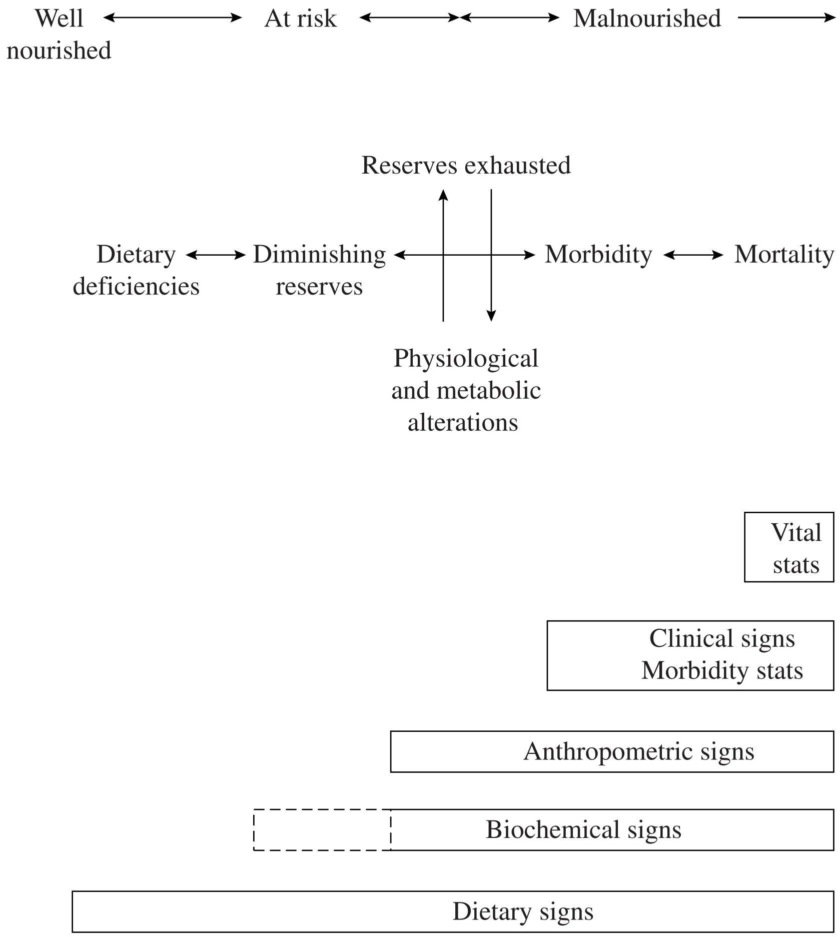
Well nourished
At risk
Malnourished
Reserves exhausted
Dietary deficiencies
Diminishing reserves
Morbidity
Mortality
Physiological and metabolic alterations
Vital stats
Clinical signs
Morbidity stats
Anthropometric signs
Biochemical signs
Dietary signs

FIGURE 7-1 The process of becoming malnourished and the place of the elements of nutritional status assessment at different stages of the process. (Derived from Sabry ZI. Assessing the nutritional status of populations: Technical and political considerations. Food Nutrit. 1977;3(4): 2–6.)

examining data on nutritional deficiencies, it is important to distinguish between those based on "biochemical" deficiencies and those based on "clinical" signs, in terms of establishing the importance or priority of the problem. Some would have it that assessment of nutritional status should be based more firmly on functionality rather than low levels of body chemicals or size. There is much truth in this, but the cutoff points to identify good and poor nutritional status from these indices are based on outcomes and impairments wherever possible.

Anthropometry plays a major role in nutritional status assessment particularly in field and clinic studies of children. Growth faltering is regarded as an early sign and symptom of poor nutrition, and nutritionists rely heavily on anthropometry for indices of nutritional status. Not all causes of impaired growth are nutritional in origin. Most commonly, growth can be impaired by disease and infection and an associated anorexia or poor appetite. The significance of this is that the first priority may be to treat concurrent infections and eradicate their causes rather than attempt refeeding or development projects in agriculture or subsistence food production. The provision of clean, protected water supplies and sanitation may also be an early priority.

In nutritional status assessment, the “growth” of a population is often described by cross-sectional measurements. There is a risk of circularity in a discussion of nutrition and growth when growth is used as a proxy for nutritional status. The interpretation of a particular size, whether a small child is normally small or growth retarded, is a difficulty, but one outside the scope of this chapter. Height, or length, is a key variable for auxologists, but nutritionists are particularly interested in growth of muscle mass, adipose tissue mass and its location, and bone mass because of the greater direct functional implications and the consequences for long-term good health.

NUTRITION AND GROWTH

The importance of nutrition for growth is well attested by clinical observations of growth reduction in conditions of reduced food intake, such as anorexia nervosa, and in intestinal malabsorption, such as is associated with untreated cystic fibrosis. At the population level, growth faltering has been observed and well documented to be associated with food shortages in conditions of civil unrest and war. However, nutritional challenges to growth rarely occupy precisely circumscribed epochs and even more rarely do they operate in a vacuum. The secular trends in growth, menarche, and skeletal maturation observed in many countries over the last 100 years are a record of the effects of previous living conditions on growth. Most commentators ascribe a key role to improvements in nutrition in these secular changes (see Chapter 9). Nutrition is one of a number of environmental influences on growth. The others include infection, poverty, poor housing, and schooling; and it can be difficult to identify and evaluate the precise contribution of nutrition to growth or growth failure. The type, duration, and intensity of the nutritional challenge influence the nature of the response in growth, as does the ecological setting. There is thus no quantitative lawlike relationship between nutrition and growth, and descriptions of the relationship tend to be either rather general or biosocial case histories.

Normal Nutrition

Maternal and fetal nutrition and nutrition in infancy, childhood, and adolescence are topics well covered in many textbooks on nutrition. Most are specific to a particular region (e.g., North America or Europe), and few are balanced according to developed country issues. The aims of this chapter do not include teaching basic nutrition, and it is not covered in any detail. Some representative texts are listed in the Annotated Bibliography.

The infant grows faster in the first year of life than at any subsequent period of life, and breast-feeding is recognized as the appropriate method of feeding the newborn and infant in the first months. The advantages expand beyond the provision of a feed nutritionally suited to the human infant that is hygienic and at the correct temperature and with a built-in supply regulator. They extend to better immune competence and more protection against gastroenteritis, ear, and chest infections, eczema, and childhood diabetes. For the mother, there is a speedier reduction in size of the uterus and a lower risk of premenopausal breast cancer, ovarian cancer, and hip fracture. For a variety of reasons, some mothers choose not to breast-feed or may be unable to breast-feed. These women should have as much support as breast-feeders and should not be made to feel guilty or inadequate.

A basic assumption is that breast milk composition has evolved to meet the nutrient needs of the infant. If the amount produced is sufficient, that is, if energy needs are met, so are nutrient needs. Breast milk intake of 850 ml/day would meet the needs of infants growing along the 50th centile until 4 months old.[6] It would meet the needs of an infant in a developing country growing along the 25th percentile for 6 months. Weaning should begin at these ages.

Breast-fed babies have in the past been found to grow more slowly in infancy than formula-fed infants in some but not all studies. This meant that breast-fed children often appeared to be growing less satisfactorily than reference growth data as the older growth reference data came from groups of exclusively or mostly formula-fed infants. There is some evidence that this difference has lessened as formula feeds have been "humanized"; that is, modified toward the composition of breast milk. Fears that formula-feeding may promote the development of widespread overfeeding and obesity have not been founded. The other major concern of infant nutrition in developed countries, the premature introduction of solid foods, is being addressed by information and education programs.

Table 7-1 shows the United Kingdom's RNI and the United States' AI for selected nutrients for children 1–10 years old. Some of the biggest differences are for calcium. There is currently no international consensus on recommendations for calcium intake. The United States currently recommends 800 mg/day for children, based on the maximal retention of calcium in bone. In the United Kingdom, lower figures of 350–550 mg/day have been recommended, but based on a factorial approach with allowances for gain, loss, and absorption.

Nutritional needs in adolescence may be, in absolute terms, greater than at any other time of life. The high rates of proportionate growth may only equal or be less than those of the first few months of life, but they persist for much longer. It is a time when individuals make more of their own choices in food, in some cases using them as part of a relationship struggle with parents and caregivers, but without necessarily too much nutritional knowledge. Independence, or the pursuit of it, may lead to behaviors, such as anorexia, bulimia nervosa, and substance abuse, that threaten nutritional integrity and hence growth. However, the growth of teenagers can be remarkably resilient to nutritional challenges, as illustrated later when considering the pubertal growth spurt in poorly nourished Indian adolescents.

Nutritional Demands of Growth

Good nutrition is of fundamental importance to growth. When food becomes limited, one of the earliest responses of the body is to retard growth; indeed, growth assessment by anthropometry is one of the most commonly used indices of nutritional status. Similarly, deficiency of a single nutrient, such as zinc, may cause growth failure. It is easy to move from this to the idea that growth is a costly process that requires most of the energy and nutrient intake. This may be true for some mammals but not for humans, with the exception of the first few months of life. Figure 7-2 shows the energy cost of growth from infancy to adulthood and the usual energy intake over this period. It can be seen that the requirements for growth make up less than 10% of the total energy intake for most of the growth period. However, as growth is in the front line of responses to nutritional challenges, problems are common.

Malnutrition

Malnutrition means bad nutrition. The term applies equally to overnutrition as to undernutrition, but it tends to be used more for the latter than the former. It has been estimated that the proportion of the world's population exhibiting overnutrition now matches that showing undernutrition. However, the sequelae of overnutrition may take their toll in adulthood; for example, as cardiovascular disease or non-insulin-dependent diabetes mellitus. In contrast, the sequelae of hunger and undernutrition—that is, increased susceptibility to infectious disease, physical and mental impairment, and possibly death—affect the young most; and undernutrition is given more prominence here.

Growth retardation in developing countries is said to be most common and most marked between 6 and 12 months of age. This timing is the intersection of infant and childhood phases of growth, a time when the system is unusually sensitive to stress or perturbation. It is also a time of high growth velocities and nutritional needs and of the troublesome period of weaning. Growth retardation at this time is most severe in infants of low birth weight. This, plus the concerns of long-term implications for health in adult life and intergenerational effects on growth, emphasize the importance of fetal and maternal nutrition. However, it must be remembered that poor fetal growth is a marker for poor socioeconomic factors in general, which lead to a more stressful and less successful life. Control for such factors is notoriously difficult, and its absence or failure seriously weaken inclusive hypotheses of intrauterine nutrition and adult disease.

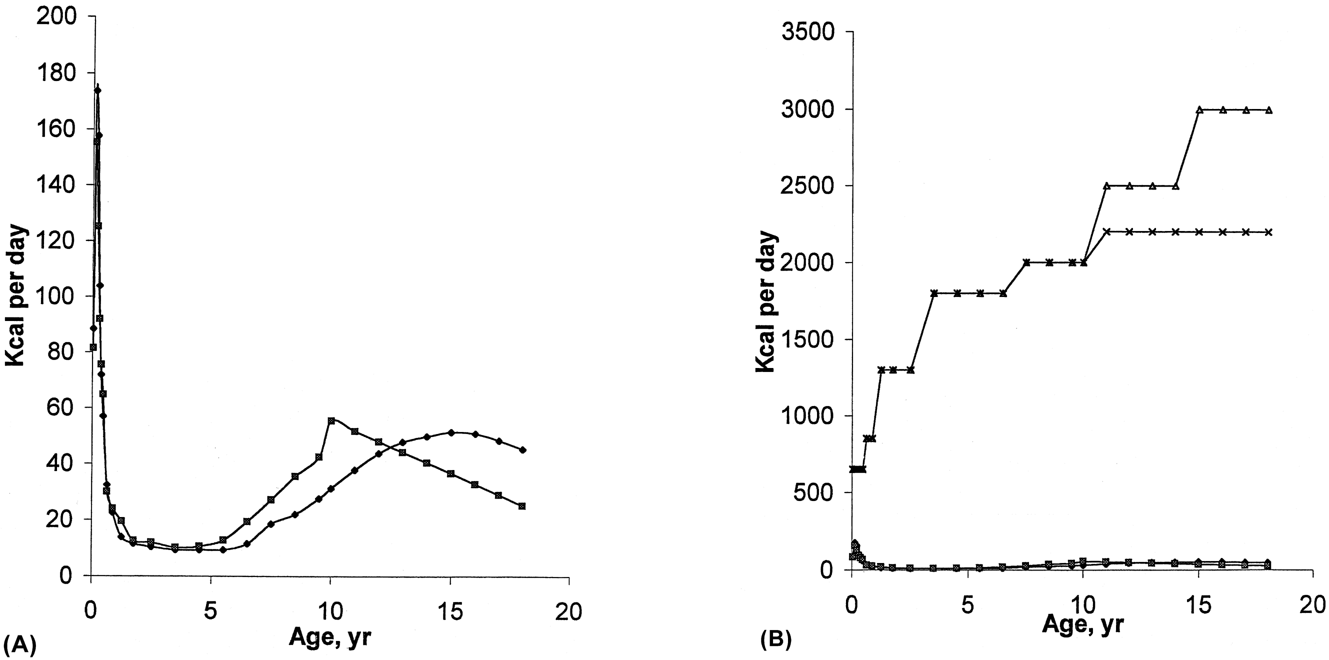

FIGURE 7-2 The energy cost of growth. (A) Cost calculated from lean and fat gains derived from the body composition data of Fomon SJ, Haschke F, Zeigler EE, Nelson SE. Body composition of reference children from birth to age 10 years. Amer J Clin Nutrit. 1982;35:1169–1175; and Guo S, Chumlea WC, Roche AF, Siervogel RM. Age- and maturity-related changes in body composition during adolescence into adulthood: The Fels Longitudinal Study. Int J Obes. 1997;21:1167–1175, and assuming an energy of fat-free mass and fat of 1.6 and 9.3 Kcal/g and an energy cost of synthesis of 15%; ◆—◆ Boys, ■—■ Girls. (B) The energy cost of growth compared to the U.S. 1989 recommended daily allowance for energy; ◆—◆ Boys, ■—■ Girls, ^—^ RDA Boys, x—x RDA Girls.

Protein-Energy Malnutrition

Protein-energy malnutrition (PEM) is the most common and important nutritional deficiency. Half the world's children are said to suffer undernutrition, mainly as protein-energy malnutrition. In its severe form, it exists as kwashiorkor and marasmus. In many African and Asian countries, 1–3% of children under 5 years old suffer severe malnutrition. In its less severe form, it appears as stunting and wasting, depending on the severity and duration of the insult. In developing countries, 10–50% of children are stunted, that is with heights more than 2 SD below reference data medians. The model of malnutrition in developing countries is of an iceberg. For every 1 case of severe malnutrition that is visible at clinics or in hospitals, there may be 15–25 moderate cases and a further 25–35 mild cases in the community. In global terms, the numbers affected may be 150 million.

According to conventional methods of classifying causes of death, malnutrition does not appear a major cause in developing countries and, consequently, receives less of the donor and national health resources. However, results from eight prospective studies in different parts of the world indicate that 42–57% of all deaths of 6- to 59-month-old children are due to malnutrition's potentiating effects on infectious disease. The relative risk of death for severe malnutrition is eightfold, for moderate fivefold and for mild two and a half times that of normally nourished children. However, more than three quarters of the nutrition-influenced deaths are attributable to mild–moderate malnutrition.

We are presented routinely with pictures of malnutrition arising from natural disasters, and it is easy to accept the myth that malnutrition results from scarcity of food. The vast majority of cases of malnutrition have roots more in economic and political considerations, many of which exacerbate any climatic or biological effects. According to the Nobel Prize–winning development economist Amartya Sen, famine has never occurred in a democracy. Inequitable distribution of resources and gender discrimination make a large contribution to malnutrition. It is estimated that 80% of undernourished children live in countries with food surpluses. Suffice to say that malnutrition rarely has its origins in a shortage of food. If we can nourish people at the poles, in the ocean depths, and in space, where no human foodstuffs grow naturally, we have the ability to nourish people in less extreme habitats.

The underlying causes of malnutrition are many, and their interrelationships are complex and diverse. There is a well-documented synergism between nutrition and infection in their effects on growth. The undernourished child is more susceptible to infection and the ill child has higher nutritional requirements at a time when they are likely to be anorexic. The interrelationships are too complicated and context specific to allow this synergism to be easily quantified. Effects on the gastrointestinal mucosa causing malabsorption may predominate. Estimates suggest that perhaps one third of linear growth failure can be ascribed to illness. However, children in rural areas of developing countries who have avoided infection to any significant extent are still 10–15 cm less than American children at 7 years old.

Developed Country Issues

Undernutrition is not a problem confined to developing or transitional societies, to civil unrest and warfare. Poverty, relative and absolute, is found in all countries. Within the United Kingdom, a member of the G7 Group of Industrialized Nations, mortality and socioeconomic differentials have widened over the last 15–20 years and adverse socioeconomic circumstances in childhood influence subsequent mortality that is independent of the continuation of the disadvantage throughout life. From the other end of the social spectrum, affluent parents with particular beliefs about food habits have caused growth retardation in their children.

Studies have been performed on the growth of children consuming macrobiotic diets in Holland, following observations that these children were lighter and shorter than a control group on an omnivorous diet.[7] Macrobiotic diets resemble those of many children in developing countries in being based on grain cereals, mainly rice, vegetables, and pulses, foods high in fiber and starch but relatively low in protein and with intakes of calcium and vitamin D substantially below Dutch RDAs. Deviations in growth began in the weaning period with partial catch-up between 2 and 4 years old in weight and arm circumference but not in height. Linear growth was associated with protein content but not energy content of the diet. The children of families that subsequently increased their consumption of fatty fish or diary products grew more rapidly in height than the other children.

These observations are significant as they illustrate that growth is nutrition sensitive even in a good environment. Much of the material concerning developing countries that follows may leave the impression that improving nutrition is not very influential, but this is because those environments contain a number of other impediments to growth.

Catch-up Growth

A key question in human biology over recent years, and one that has received much attention, is to what extent can a growth-retarded child catch up. Martorell, Kettel Khan, and Schroeder hold that stunting (low height for age) arises from events early in life, and once present, it remains for life.[8] The contrary view of Tanner is that the undernourished child slows down and waits for better times.[9] Tanner considers that, “in a world where nutrition is never assured, any species unable to regulate its growth in this way would long since have been eliminated.” Obviously, if a child remains in the environment that led to stunting, it is unlikely that this will be conducive to improvements in growth. However, Adair recently described catch-up between 2 and 12 years of age in Filipino children staying in the same environment.[10] Severe stunting in the first 2 years was associated with low birth weight, which significantly reduced the likelihood of later catch-up. Positive attributes associated with catch-up were taller mothers, being the first born, and fewer siblings, which illustrates again the actions of intervening nonnutritional factors.

There is a remarkable feature in the growth of children in India, the Gambia, West Africa, and elsewhere who were stunted, in some cases severely stunted, before 5 years old and remain stunted at 18 years old. The growth increment between 5 and 18 years may match that of western children.[11] The growth pattern is not the same, as puberty is later and prolonged. It is not clear how this comes about. It is almost as though the last chance for catch-up is taken. Perhaps, growth in height is replaced by another factor, growth in weight or physical activity, in the front line of impairments.

In contrast to height deficits, weight deficits increase from childhood to adulthood in almost all populations with childhood growth retardation. This may have significant and long-lasting consequences as weight for age and weight for height may be more important than height per se in terms of functional outcomes such as work capacity, earning power, and employment. Linear growth has tended to receive more attention by auxologists than growth in mass, but this bias decreased in recent years.

Improvements in the environment result in catch-up growth, but such improvements are not common. Reports of the long-term effects of treating children with malnutrition provide evidence of catch-up, even though treatment may be for only a short period and the child returns to the same environment. Community-based supplementation studies provide better evidence of what can be achieved in the habitual environment, as described next. Any prediction as to whether catch-up growth will occur in an individual or population requires a full environmental assessment.

Relocation to better environments in the form of migration or adoption involves changes in the environment not restricted to nutrition. Studies of refugees and adoptees from South and Southeast Asia have shown accelerated growth rates, but it is not yet clear if these translate to increased adult stature. There is some evidence of accelerated puberty, which may have the effect of shortening the growth period and curtailing adult stature.

Supplementation Studies

Supplementation is taken to be an addition to a diet to make up all or part of a deficiency. It can vary according to the type, amount, and duration; hence, a dose-response effect should be observed. Thus, it is a classical research design of high internal validity to demonstrate the presence of undernutrition and its effects on growth. This is also a common approach to improving maternal and child health. It might be thought that supplementing the diet of children and mothers in populations with low growth rate would inevitably result in improved growth. However, when this is attempted, the effects are usually much smaller than expected, and growth never achieves the levels of the most affluent groups in the same population or the median values in western reference data.

Several extensive supplementation studies are described in the literature. One such is the Institute of Nutrition of Central America and Panama (INCAP) longitudinal study of the effects of chronic malnutrition on growth and behavioral development that began in 1969. It is unusual, in having a follow-up component several years after supplementation ended.[12] The study was conducted in four villages, which began with small and light mothers on low dietary intakes and with weight gains in pregnancy half those of well-nourished women; 15% of the infants died in the first year of life. Two types of supplement were provided to children up to 7 years old. Two villages selected at random were provided with atole, a protein-energy supplement, and the other two with fresco, a no-protein supplement with one third the energy content of atole. Both supplements contained minerals and vitamins, and preventative and curative medicine were provided to all villages. Supplement take-up was voluntary and so varied widely, but this allowed a dose-response approach to the analyses using multiple regression and for confounding factors to be taken into account.

Birth weights increased, but only by some 7 g per 10 MJ of supplement. However, low birth weight and infant mortality fell by a half in those with high supplement intakes. Energy intake was more important than protein for these improvements. In 0- to 3-year-old children, greater supplementation was associated with better growth in supine length and weight but not limb circumferences or skinfold thicknesses. In the highest supplementation group, these differences were 1 kg and 4 cm at 3 years old. Supplementation of 420 kJ (100 kcal) per day was associated with additional length gains of 9 mm in the first year, and 5 and 4 mm in years 2 and 3, but had no effect after 3 years of age. Children from supplemented villages continued to weigh more, be taller, and to have higher lean mass at adolescence, although differences in height were reduced compared to those at 3 years old. Other studies have been analyzed differently but show similar finding when an age-stratified approach is used. Therefore, the effects of supplementation are small and less than expected. The supplemented children did not approach the levels of height and weight seen in more affluent groups or in some other developing countries; and as only some 15% of the energy of the supplement is utilized in growth processes, the fate of most of the supplement is not clear. These data come from research studies that are likely to be more successful than feeding programs because of the enthusiasm of the workers.

There are several possible explanations for this.[13] It may be the result of poorly designed and implemented feeding programs. Alternatively, it may be that the hypotheses and models of the processes involved have been unduly simplistic and inappropriate. The supplement may not reach the intended recipient or it substitutes for rather than supplements the habitual diet. "Leakage" and substitution should not be seen as failures of supplementation, as they may have benefits, albeit away from the intended recipient. The supplement may lead to increased activity, with the benefits of play and fitness and social competence, rather than growth.

Lindsay Allen, in her exemplary review of nutritional influences on linear growth, concluded that there was a lack of clear, consistent evidence and that supplementation of zinc, iron, copper, iodine, vitamin A, or indeed energy or protein alone benefited linear growth in growth faltering in developed countries.[14] In some studies, improvements were seen; in others, weight gain alone was affected; and in still others, there was no effect whatsoever. However, most of these studies have been on children older than the age at which growth faltering is most rapid. Alternatively, multiple deficiencies may be the cause of growth faltering. Except in the case of iodine, low energy diets are usually low food diets, which means low nutrient diets; that is, multiple nutrient deficiencies.

Growth retardation due to zinc deficiency was first described in the Middle East in the 1960s. Zinc deficiency was associated with high fiber, low protein diets and with parasitic infections. High-level supplementation of zinc was necessary to achieve improvements in growth presumably because the high phytate content of the high fiber diets reduced its bioavailability. Supplemental zinc has been given to low height-for-age well-nourished children in developed countries with variable effects. Linear growth is often improved but not weight gain. Often, there is no reason for these children to be zinc deficient unless they have unusually high dietary requirements for zinc. The role of zinc in the linear growth retardation of developed countries requires further work.

The most widespread dietary deficiency in North America is of iron. The incidence of childhood anemia has been falling at a time when iron-fortified formulas and cereals have become widespread and supplemental food programs have been introduced. Linear growth usually improves in response to iron treatment in anemic children. Iron deficiency also has nonhematological effects.

Nonnutritional factors, such as the social, economic, and biological environments, are important in determining the response to supplementation. In each community, different factors may operate, and there may be no circumventing the need for a full description of the ecology of the community. Our hypotheses and our models and methods of analyses may need to be refined to identify better what needs to be measured. There are, however, limits to the number of variables that can be studied, determined by the cost and quality of the data obtained. However, these studies provide good examples of the fact that diet does not operate in isolation but in concert with other environmental challenges, such as disease, poor schooling, and general deprivation. (Some of these issues are described in Chapter 8, “Environmental Effects on Growth,” and Chapter 9, “Social and Economic Influences on Growth and Secular Trends.”) The answer would then seem to lie in general environmental enrichment. But, in the absence of endless resources, the key deprivations in each particular case need to be established by ecological study and a more targeted approach to entitlement, enrichment, and empowerment adopted.

Overnutrition

Malnutrition in the form of overnutrition or obesity is a major nutritional problem in the western world and is becoming common in other parts, too. Here, too, the obvious assumption, that obesity has its origins in gluttony and that the appropriate remedial action is to reduce dietary intake, may not be valid. Obesity can arise only through a positive energy balance, but this does not need a high energy intake to develop. Low levels of physical activity, inactivity with roots in car use and leisure time TV viewing or computer and games console use, is a major etiological factor. Any lowering of energy intake in such children would have an increased risk of precipitating nutrient deficiencies, although changes in the types of macronutrients consumed, such as less fat and a lower energy-dense diet, may be beneficial. Rather, the negative energy balance should be brought about in the main by increased physical activity. From this will flow all the other major health benefits associated with increased activity, fitness, and altered body composition, including increased self-esteem. However, the difficulty of achieving and maintaining weight loss should not be underestimated but should be used as a motivation for avoiding overweight and obesity.

One problem in the area of childhood obesity is how to define it. In adults, we have imperfect but widely accepted indices, such as body mass index and waist circumference, for which particular values or cutoffs have been associated with a variety of risk factors, of morbidity and mortality. It then is possible to specify "healthy" or "recommended" levels. In children, the median value and other percentiles vary with age and not always in a linear or predictable way; and as yet, few studies have linked these indices to risk factors and very few with outcomes such as morbidity and mortality. Because of this, *obesity* may then be defined on a statistical basis, such as BMI above the 85 percentile, which is not entirely satisfactory. (See Chapters 16 and 18 on "The Assessment of Human Growth" and "Growth References and Standards.") Bearing in mind the difficulties in assessing the global prevalence of obesity in children and adolescents because of the differing indices employed, longitudinal studies suggest it has doubled in the last 20 years. The measurement and long-term health risks of childhood and adolescent fatness have been well reviewed recently.[15]

The extent to which obesity in childhood persists into adulthood seems to depend on the time interval between the occurrence in childhood and adulthood. Thus, obesity in adolescence seems more persistent than obesity in childhood. This is the "recency" effect. Until now, most obese adults were not obese as children, but as the prevalence rises, this finding may change.

TRANSITIONS IN NUTRITION AND GROWTH

It is unlikely that humans would have evolved so successfully if they had selected inappropriate diet types. However, it is equally true that the rate of adoption of new and manufactured foods (decades) is much greater than the rate of human evolution (tens of generations), and we cannot assume that we are well adapted to contemporary foodstuffs and diet types. Some 50% of dietary energy in the world is from cereals or cereal products, but only in evolutionarily recent times has this become the case. The domestication of plants and of animals, begun 10,000 B.P., that is, 500 generations ago, altered the diets of humans more than any previous subsistence change. Our societies and cultures have changed, too, and in ways such that technology and globalization have not been uniformly beneficial. Therefore, nutritional problems, albeit different problems to those of the distant past, exist in conditions of affluence.

Nutrition is usually ascribed a key role in the improvements in growth in Europe and other parts of the world over the last centuries. The evidence for this is much less extensive and definitive than we would like, and improvements in growth would not have occurred without concomitant improvements in housing, sanitation, and health provision. (Secular trends in growth are discussed in Chapter 9 on "Social and Economic Influences on Growth and Secular Trends.") How these transitions will continue in the future and what new ones will appear in the short or long term is in the realm of prediction but something for which the students of today may have the answer in their lifetime. A major epidemiological interest of the present centers on the hypothesis that maternal and fetal undernutrition program the body to respond to subsequent affluent nutrition in ways that lead to a number of degenerative diseases. If true and if mothers and fetuses are no longer exposed to undernutrition in developed countries, then we may see a reduction in the incidence and mortality from these degenerative diseases, as is happening already in much of the developed world. However, much of the rest of the world has yet to experience the first stage of this transition. In many parts of Africa, some of which have a host of other health problems such as the prevalence of HIV infection, nutritional health seems set to fall, at least in the short term. This will have an impact on the growth of the next generation of children.

ANNOTATED BIBLIOGRAPHY

Nutrition Textbooks

There is no shortage of choice of nutrition textbooks for U.S. students. I am not familiar enough with all of them in their most recent editions to be able to identify one or two for specific mention. Most are very student friendly, well written and illustrated, with good structure and development of material, end of chapter summaries, assessment activities, and nowadays, lists of Web-based resources. There is some variation in the amount of basic biochemistry and anatomy and physiology that is included. Two examples on my shelf are G. M. Wardlaw and P. M. Insel's *Perspectives in Nutrition* (St. Louis: Mosby, 1993) and E. N. Whitney and S. R. Rolfes' *Understanding Nutrition* (Minneapolis: West Publishing Co., 1996). One disadvantage of these types of books is that they are written at length, typically more than 500 pages, and in detail, although not necessarily in great depth, for students of nutrition.

Nutrition Textbooks for Nonnutritionists

Barasi ME. Human Nutrition; A Health Perspective. London: Edward Arnold, 1997. This book is recommended for any student with no background in nutrition but taking it as part of a wider program. It is well-written and tackles the fundamental issues clearly and concisely. There is little on Third World issues.

Gibson RS. Principles of Nutritional Status Assessment. New York: Oxford University Press, 1990. The word *principles* in the title of this book belies the detail and scope of its contents (691 pp.). It is a reference book par excellence, well written and with copious appendices of anthropometric and other reference data. It covers the dietary, anthropometric, and biochemical approaches to nutritional status assessment and has a short section on clinical assessment. Its publication was more than 10 years ago, and inevitably, some sections, such as that on body mass index, need updating. The emphasis is more on hospital and laboratory assessment than field surveys in the Third World. In the latter context, more consideration of environmental and ecological factors is warranted.

Mann J, Truswell AS. Essentials of Human Nutrition. Oxford: Oxford University Press, 1998. This book sets out to meet the needs of clinicians, health professionals, and teachers and, according to the publishers, is proving to be very successful. However, it, too, is over 600 pages. Some of the individual chapters can be strongly recommended. Rosalind Gibson's "Dietary Assessment" and "Determining Nutritional Status" covers the material of her book, described later, in a less detailed manner. Stewart Truswell's "Nutritional Recommendations for the General Population" is a tour de force historical and comparative account of dietary recommendations and guidelines. It includes answers to most questions on the principles of establishing recommendations. Better chapters on childhood and adolescence and protein-energy malnutrition are found elsewhere. The standard works on protein-energy malnutrition include J. C. Waterlow's *Protein Energy Malnutrition* (London: Edward Arnold, 1992).

Webb GP. Nutrition: A Health Promotion Approach, 2nd ed. London: Arnold, 2002. This book is recommended for students of human biology because it treats well the methods of nutritional surveillance and research and, in particular, the types and strengths of evidence. There is little on Third World issues.

A good bookmark for nutrition links is http://www.nutsoc.org.uk/links.htm.

Nutrition topics at the National Library of Medicine are at http://www.nlm.nih.gov/medlineplus/foodnutritionandmetabolism.html.

Nutrition and Growth in Bioanthropology, Growth, and Human Biology Texts

Bogin B. Patterns of Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1999:268–282. The biocultural approach to growth and nutrition by this informed and readable author ensures that the relationships of nutrition and growth are considered within the context of the wider environment.

However, it would be easy to gain the idea from the section on "the milk hypothesis" that there is something specific to milk and its effects on growth of undernourished children not shared by other good sources of nutrients. In practice, its advantages are likely to be in nonnutritional terms such as cost and availability.

Eveleth PB, Tanner JM. Worldwide Variation in Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1990:191–198, 219–223. This is a succinct description of nutrition and growth in infancy and adolescence located in a classical account of environmental influences in growth.

Tanner JM. Foetus into Man, 2nd ed. Ware, UK: Castlemead Publications, 1989:129–140. There is a short informative account of the effects of nutrition on growth and the tempo of growth which is a useful introduction to the topic. The section on experimental models is unusual in such accounts but illustrates well what can be learnt from laboratory-based studies.

Ulijaszek SJ, Strickland SS. Nutritional Anthropology: Prospects and Perspectives. London: Smith-Gordon, 1993:119–131. There is a short section on nutrition and growth but much else of interest and relevance throughout the book, including the consequences of small size, seasonality, and growth and transitions in subsistence.

Ulijaszek SJ, Johnston FE, Preece MA. The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998. Many entries are relevant to nutrition and growth in the sections on infant feeding and growth (pp. 320–325), nutrition (pp. 325–333), and elsewhere. These provide useful introductions to a number of topics under these headings. There are extensive lists of up-to-date references.

Zerfas AJ, Jelliffe DB, Jelliffe EFP. Epidemiology and nutrition. In: Falkner F, Tanner JM (eds). Human Growth: A Comprehensive Treatise, 2nd ed. Vol. 2, Postnatal Growth. New York, London: Plenum, 1986:475–500. Although much new data has been collected since this chapter was published, its content and structure, with emphases on methods and approaches to the effects of protein-energy malnutrition on human growth, are exemplary and a valuable source of guidance. The three-volume series is widely available and repays consultation.

Research Reports and Reviews, Including Individual Chapters

The International Dietary Energy Consultative Group (IDECG) produced several research reviews arising from workshops that have the advantage of being available without charge from IDECG or at the United Nations University Web pages (http://www.unu.edu/unupress/food/foodnutrition.html) or as supplements to widely available journals. They are included in this list because of their availability and because they have several papers in each report relevant to this chapter. They are also written by experts in the field and well done. IDECG reports are available from IDECG Secretariat, c/o Nestle Foundation, P.O. Box 581, 1001 Lausanne, Switzerland. (Note: It might be better if lecturers obtained copies from IDECG and placed them in libraries rather than each individual student requesting copies.)

Allen LH. Malnutrition and human function: A comparison of conclusions from the INCAP and nutrition CRSP studies. J Nutrit. 1995;125(Suppl 4):1119S-1126S or Martorell and Scrimshaw IDECG report. This article reviews the evidence that growth stunting occurs early in life and is accompanied by functional impairments. The CRSP studies in Kenya, Egypt, and Mexico suggest poor growth is associated with multiple micronutrient deficiences and have been influential in diverting attention from protein-energy malnutrition to other nutrient deficiences. This was not investigated in the INCAP studies whose children were much more malnourished and stunted.

Allen LH. Nutritional influences on linear growth: A general review. Euro J Clin Nutrit. 1994;48(Suppl 1):S75–S89 or Waterlow and Schürch IDECG report. The paper reviews what is known about the effects of specific nutrient deficiencies on growth faltering. There is no clear, consistent evidence that supplementation benefits linear growth. This may be because the children studied have been beyond the age when growth faltering is most rapid.

Assessment of childhood and adolescent obesity. Amer J Clin Nutrit. 1999; 70(Suppl 1):123S–173S. Considerations of height, weight, and body mass index dominate this recent collection of papers. Visceral fat is discussed by Goran and Bower in relation to disease risk in children and adolescents.

De Onis M, Villar J, Gulmezoglu M. Nutritional interventions to prevent intrauterine growth retardation: Evidence from randomised control trials Euro J Clin Nutrit. 1998;52(Suppl 1):S83–S93 or in the Scrimshaw and Schürch IDECG report. At present, no effective nutritional interventions have been demonstrated to reduce the risk of intrauterine growth retardation with the possible exception of balanced protein-energy supplementation. The authors emphasize the gap between the size of the problem and the quantity and quality of the data. Further work is necessary on zinc, folate, and magnesium with larger samples.

Golden MHN. Is catch-up possible for stunted malnourished children? Euro J Clin Nutrit. 1994;48(Suppl 1):S58–S71 or Waterlow and Schürch IDECG report.

Himes JH, Story M (eds). Assessment of childhood and adolescent obesity. Inter J Obes. 1999;23(Suppl 2):S1–S58–S64. The expected issues of identification, prevalence, risks, physical activity, prevention, and treatment are covered mainly with a North American perspective. The complexity of the etiology of obesity is described by a new model for treating childhood obesity.

Leon DA. Fetal growth and adult disease. Euro J Clin Nutrit. 1998;52(Suppl 1):S72–S82 or in the Scrimshaw and Schürch IDECG report. This paper is said to put the work of Barker and colleagues into the realm of hypothesis generation as opposed to hypothesis testing. This is because of the use of a retrospective approach to an issue with multiple causes. The conclusion of this thoughtful, well-written paper is that, "At the present time the foetal origins hypothesis should be regarded as an area for basic bio-medical research. It is difficult at this stage to draw strong public health conclusions with the limited state of knowledge."

Martorell R, Kettel Khan L, Schroeder DG. Reversibility of stunting: Epidemiological findings in children from developing countries. Euro J Clin Nutrit. 1994;48(Suppl 1):S45–S57 or Waterlow and Schürch IDECG report.

Martorell R, Scrimshaw NS. The effects of improved nutrition in early childhood: The Institute of Nutrition of Central America and Panama (INCAP) Follow-up Study. Available as J Nutrit. 1995;125(Suppl 4):1027S–1138S or as an IDECG report. The INCAP study and its follow-up are the first comprehensive long-term evaluation of a nutrition intervention aimed at mothers and children in a developing country. These peer-reviewed papers might normally have been published individually in a variety of journals and it is a great service to the student that they appear in one volume.

Norgan NG. Chronic energy deficiency and the effects of energy supplementation. In: Schürch B, Scrimshaw NS (eds). Chronic Energy Deficiency; Consequences and Related Issues. Lausanne: IDECG, 1987. This paper reviews the effects of dietary supplementation in chronic undernutrition and considers why supplementation has small effects. It identifies the need to move from simple main effects models to studies of the indirect multistage processes involved and the indirect effects on the family.

Schürch B, Scrimshaw NS. Chronic Energy Deficiency; Consequences and Related Issues. Lausanne: IDECG, 1987. The first IDECG report summarized knowledge on how chronic energy deficiency can affect pregnancy, lactation, and childhood; work capacity and performance; and social and economic development.

Scrimshaw NS, Schürch B. Causes and consequences of intrauterine growth retardation. Available as a Euro J Clin Nutrit. 1998;52(Suppl 1):S1–S103 or as an IDECG report. This is a timely report, given the importance now being attached to early nutrition reducing infant and childhood malnutrition and the hypothesis of effects arising in adulthood. It includes a systematic review of 126 randomized control trials with 36 kinds of interventions.

Waterlow JC, Schürch B. Causes and mechanisms of linear growth retardation. Available as Euro J Clin Nutrit. 1994;48(Suppl 1):S1–S216 or as an IDECG report. Much is known about the epidemiology and natural history of stunting. Much less is known about the actual causes and mechanisms. There is epidemiology here, too. The papers on catch-up growth by Martorell, Kettel Khan, and Schroeder and by Golden should appear in any reading list on the topic.

The home page of the International Obesity Task Force with a section on childhood obesity and links to other obesity sites is at http://www.iotf.org./.

REFERENCES

These have been included in the text to support or as sources of statements. Not all are annotated, rather their significance is indicated by their context.

1. FAO, WHO, UNU. Energy and Protein Requirements. Technical Report Series No. 724. Geneva: World Health Organization, 1985. Useful as a source of information on the methods adopted to set protein and energy requirements internationally and those requirements.
2. Department of Health. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on Health and Social Subjects No. 41. London: HMSO, 1991. This report provides the current recommendations for the United Kingdom. There are links to pages on the U.S. dietary reference intakes, including the 1999 and 2000 updates, at http://www.nal.usda.gov/fnic/etext/000105.html (March 29, 2000). FAQs about DRIs and their interpretation appear at The National Academies Institute of Medicine at http://www4.nas.edu/IOM/IOMhome.nsf/pages/FNB+FAQ+DRI and +Uses (March 20, 2000). U.S. Department of Agriculture Center for Nutrition and Policy and Promotion has a website at http://www.usda.gov/cnpp/.
3. http://www.nichd.nih.gov/milk/milk_fact.htm (March 28, 2000).
4. Norgan NG. Measurement and interpretation issues in laboratory and field studies of energy expenditure. Amer J Hum Biol. 1996;8:143–158. The methods for measuring energy expenditure are described and critically appraised. Variation and adaptation in energy expenditure are considered in the context of discriminating between these and honest error, particularly in activity where many of the problems arise.
5. Food Guide Pyramid for Young Children, March 25, 1999. http://www.usda.gov/cnpp/KidsPyra/index.htm (15 March 2000).
6. Whitehead RG, Paul AA. Long-term adequacy of exclusive breast feeding: How scientific research has led to revised opinions. Proc Nutrit Soc. 2000;59:17–23. Improved nutritional and anthropometric guidelines are provided for the assessment of lactational adequacy and for when weaning may be initiated. These are based on revised dietary energy requirements.
7. Danielle PC, van Dusseldorp M, van Staveren WA, Hautvast JGAJ. Effects of macrobiotic diets on linear growth in infants and children until 10 years of age. Euro J Clin Nutrit. 1994;48(Suppl 1):S103–S112 or as the Waterlow and Schürch IDECG report.
8. Martorell R, Kettel Khan L, Schroeder DG. Reversibility of stunting: epidemiological findings in children from developing countries. Euro J Clin Nutrit. 1994;48(Suppl 1):S45–S57 or as the Waterlow and Schürch IDECG report.
9. Tanner JM. Foetus into Man: Physical Growth from Conception to Maturity, 2nd ed. Ware, UK: Castlemead Publications, 1989:130.
10. Adair LS. Filipino children exhibit catch-up growth from age 2 to 12 years. Journal of Nutrit. 1999;129:1140–1148.
11. Satyanarayana K, Nadamuni Naidu A, Narasinga Rao BS. Adolescent growth spurt among rural Indian boys in relation to their nutritional status in early childhood. Ann Hum Biol. 1980;7:359–365.
12. Martorell R, Scrimshaw NS. The effects of improved nutrition in early childhood: The Institute of Nutrition of Central America and Panama (INCAP) Follow-up Study. J Nutrit. 1995;125(Suppl 4):1027S–1138S or as an IDECG report.

13. Norgan NG. Chronic energy deficiency and the effects of energy supplementation. In: Schürch B, Scrimshaw NS. Chronic Energy Deficiency; Consequences and Related Issues. Lausanne: IDECG, 1987:59–76.
14. Allen LH. Nutritional influences on linear growth: A general review. Euro J Clin Nutrit. 1994;48(Suppl 1):S75–S89 or as the Waterlow and Schürch IDECG report.
15. Power C, Lake JK, Cole TJ. Measurement and long-term health risks of child and adolescent fatness. Inter J Obes. 1997;21:507–526. It is argued that anthropometric measures are practical for large-scale epidemiological studies. The child-to-adult adiposity relationship is well documented, although the prediction of adult adiposity is only moderate. This indicates that prevention should be population based rather than targeting fat children.

8

ENVIRONMENTAL EFFECTS ON GROWTH

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INTRODUCTION

Diet, nutrition, and socioeconomic resources are often considered prime influences on human physical growth and development. There are, however, many other influences, since growth and development are sensitive to a wide variety of features of the environment. Among the most-often studied are features of the natural environment (climate, temperature, and altitude). Now we must add anthropogenic features, such as air pollution, metals (mercury, lead), pesticides and herbicides (such as DDT and dioxin, a component of Agent Orange, a herbicide), and energy (radiation and noise). Most anthropogenic factors are recent developments and may pose adaptive challenges that are reflected in patterns of growth.

The study of human growth in relation to the natural environment is one of the fundamental research areas in the study of human variation and adaptation. By the mid-twentieth century, patterns of growth that were responses to the physical environment, including slower maturation and reduced growth, were considered adaptive; that is, relatively beneficial to the individual by providing some benefit in terms of survival and reproduction. While these benefits have rarely been measured, the theory that growth is a way for individuals to adapt to their immediate physical environment has been around since the 1960s.[1] Therefore, the idea that growth responses are part of the adaptive potentialities of *Homo sapiens* is found in virtually all texts on human biological adaptation.[2–4]

The view that reduced or slow growth can be an adaptation to the physical environment, and therefore beneficial to the individual, is different from the view that slow growth is a direct result of adverse circumstances, a view usually applied to reductions in growth related to diet or socioeconomic status. Tanner, who is arguably the world's expert on growth and development, has championed the use of child growth as an index of community well-being and the equality of growth among different social groups as a measure of the egalitarian distribution of health resources. In this view, slow or less growth indicates poorer health and the lack of adaptation in the face of nutritional or social disadvantage and adversity.

Therefore, researchers use two general and somewhat contradictory interpretations of environmentally influenced growth patterns. This chapter focuses on environmental influences on growth, including factors that are part of the physical environment and anthropogenic factors. Because of this dual focus, we consider the contradictory interpretations of growth after reviewing the relevant data on growth and the environment.

Research Design Issues

A review of studies of growth patterns in relation to environmental factors reveals several issues in the design of growth studies. Foremost among these is the issue of balanced precision. *Balanced precision* refers to the idea that the independent variable (the "cause") and the dependent variable (the "effect") should be measured with equal precision. The earliest growth studies examined size (the dependent variable) in relation to age (the independent variable). Early work on populations without birth records and calendars demonstrated the importance of measuring age and size with reasonable and equal accuracy. Today, studies of growth and the environment require accurate and reliable measurements of both individual growth and the environmental factors, but this is not always achieved. Measuring the environment can be easy or difficult. It is straightforward when the environmental factor is not modified by behavior or culture, and everyone living in one community has basically the same exposure (e.g., high-altitude studies). It is more difficult to measure chemical exposure because individuals in a single community can vary greatly in level of exposure. Some chemicals leave long-term residues in the body that can be measured retrospectively to estimate past exposure; for example, lead measured in blood and bone. However, other chemicals leave little trace of past exposure. Exposure to energy, such as radiation or noise, leaves no residue, and this makes retrospective studies very difficult. Technological advances may enable better measures that will allow more retrospective work in the future. For now, the study of environmental influences on growth is limited by our ability to measure environmental factors, and the information reviewed here should be understood as a limited picture wrested from substantial difficulties measuring the environmental factors of greatest concern to human well-being.

TEMPERATURE AND CLIMATE

Climate appears to influence growth and development, helping to determine body size and proportions. According to Bergmann's and Allen's rules, body size and proportions of warm-blooded, polytypic animals are related to temperature. Allen's rule states that longer extremities and appendages relative to body size are found in warmer climates, while the reverse is true in colder climates. Bergmann's rule states that a larger body size would be expected in colder versus warmer climates. The extent to which these rules apply to human body shape and is achieved through growth and development is discussed here.

Ample statistical evidence supports a relationship between adult size and shape that is consonant with Bergmann's and Allen's rules. Roberts[5] examined published data on body dimensions of multiple samples of males from around the world and correlated the sample means to measures of local temperature. There is a significant negative correlation between body weight and mean annual temperature, as well as a negative relationship between sitting height as a proportion of total height and temperature (see Figure 8-1). Newman[6] tested Bergmann's and Allen's rules through examination of aboriginal males in North and South America spanning 1000 years and observed a clinal distribution of body size. According to Newman, the smaller statures observed near the Equator supports Bergmann's rule, and the shorter legs among the Inuit supports Allen's rule. Finally, Schreider demonstrated that amount of body surface area tends to increase from cold to hot climates.[7] These

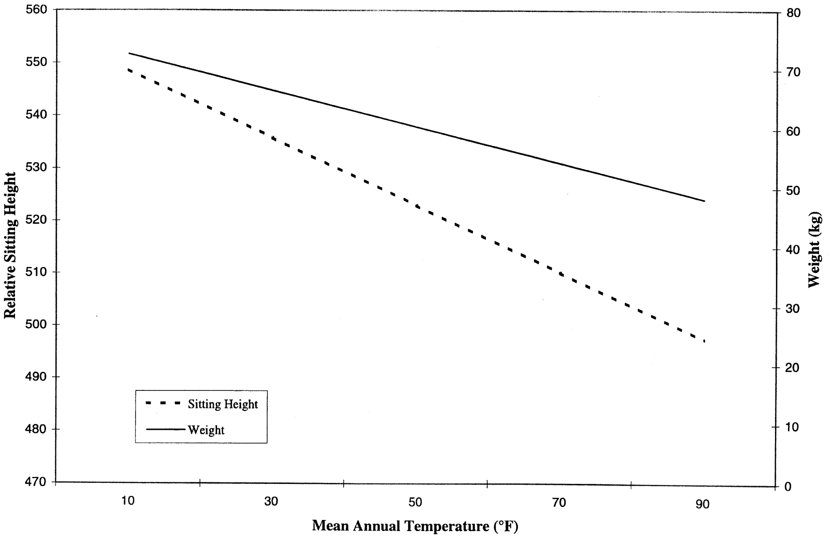

FIGURE 8-1 Relationship between mean annual temperature and body weight and relative sitting height. (Source: Adapted from Roberts.[5])

results indicate that in colder climates humans weigh more and have shorter legs relative to trunks, supporting Bergmann's and Allen's rules. There are some exceptions to this generalization, such as the pygmy populations in equatorial Africa. These exceptions may be due to using a general measure of climate (mean annual temperature) that is not the factor having the greatest impact on size, to recent population migrations, or to recent changes in nutrition that affect body size and shape.

The relationships observed between body proportion and environmental temperature can be explained in terms of the body's thermoregulatory process. In hot environments, heat dissipation is crucial to avoid hyperthermic stress, or overheating. A body that has greater surface area relative to total body size or volume more efficiently dissipates heat produced by the body's metabolism and activity. One method through which heat is lost is convection, which is the transfer of heat from the body to the environment through the movement of air over the body; thus, a greater surface area over which wind can pass is beneficial to humans in hotter climates. The reverse is true for cold environments, where heat retention is important to avoid hypothermia; thus, less surface area through which heat would be lost is more adaptive.

The small stature and low body mass of populations in tropical rainforests, for example, the pygmies in Africa, is an adaptive body shape, because the high humidity in these environments limits the effectiveness of sweating, which dissipates heat through evaporation. The smaller body mass of these populations minimizes heat retention.[7]

Crognier studied the relationship between climate and anthropometric measurements in 85 East African, European, and Middle Eastern populations.[7] He found that mean annual low temperature was strongly correlated with cranial measurements, but postcranial measurements were strongly correlated to heat and dryness. As a possible explanation for these findings, Crognier suggested that cultural adaptations to cold, such as clothing and fire, have been present in human societies long enough to have reduced the selective pressure due to cold on physical traits, but cultural adaptations to heat are less effective. Crognier also suggested that the correlation between cold and head shape could be due to the improved heat retention of brachycephalic (rounder) head shape found in colder climates; however, this argument may not fully account for the phenomenon because cultural practices that protect the head (e.g., hats) are available in cold environments. In addition, the Inuit of the Arctic are as dolichocephalic (longer heads), as are Africans, suggesting that head shape is not related to environmental temperature. Finally, other practices can influence head shape; for example, infant sleeping position can affect ultimate head shape. Also, Boas showed that skull shape is highly plastic and can change in only one generation. Children of immigrants to the United States at the end of the nineteenth century were shown to have a different head shape than their parents.[7] Thus, many environmental factors can play a role in shaping head form, and temperature may be only one.

The focus on the effects of temperature have primarily been on adult form; however, Malina and Bouchard[8] suggest that the typical body shapes associated with extremes in temperature have implications for development. These observations would suggest that either growth in hot environments is prolonged, since there is an association between delayed maturation and a linear body type, or that growth in cold environments is shortened, because of the relationship between a stocky body type and early maturation. Studies of the mean age at menarche, however, contradict this conclusion, because a negative correlation to annual mean temperature has been observed indicating that maturation occurs earlier in hotter climates.[5,8]

Eveleth[9] conducted a longitudinal study of well-off American children in Brazil to determine the effects of the hot climate on growth. She observed that the Rio children weighed less than U.S. children from Iowa and that the Rio children had less weight for height than the U.S. children, indicating a more linear body form in Brazil, as predicted from Bergmann's and Allen's rules. Limb growth also was more linear and less stocky, with more surface area to volume. This growth of shape is consistent with expectations from Bergmann's and Allen's rules. Age at menarche, however, did not differ between the Brazilian and U.S. populations, indicating that the populations were maturing at similar rates.

In humans, there appears to be a general relationship between climate and body size that roughly adheres to Bergmann's and Allen's rules. Human populations in cold climates, such as the Inuit, are generally shorter and stockier than populations in hot climates, such as the Bushmen in Africa, who are more linear.

SEASON

Seasonal variation in growth rates has been observed in healthy children. A classic study by Palmer[10] showed that, at temperate latitudes, growth rates for height are greater during the spring and summer months, while rates of weight gain are greater during the fall and winter. The greatest increases in weight are often in September through November, and can be up to five times the weight gain in the minimal months from March to May.[11] Approximately two thirds of the annual weight gain occurs between September and February. This seasonal rhythm in weight gain is not established in children until about 2 years of age.

Height growth, on the other hand, reaches its maximum from March through May. The average velocity is 2–2.5 times the average velocity during September through November, the period of minimal height growth.[11] Finally, one study suggested that minimum weight gains and maximum height gains occur simultaneously.[12] It is worth noting that these are seasonal trends in the average growth velocities. Individual patterns of growth do not necessarily conform to these seasonal peaks in growth, in fact the timing of individual peaks in growth can vary significantly.[11]

Seasonal variation in growth is not limited to temperate zones, and variation in growth rates between dry and rainy seasons has been observed in tropical climates. Bogin[13] examined patterns of growth in height for children in Guatemala City and observed that preadolescent boys and girls and postadolescent boys follow a seasonal pattern, but adolescent children do not. Approximately 75% of the preadolescent children and 65% of the postadolescent boys reached a maximum rate of growth during the dry season and a minimum rate during the rainy season. Approximately 25% of the preadolescent children and 33% of the postadolescent boys demonstrated an opposite pattern of growth.[13] The absence of an effect during adolescence may be due to the pubertal growth spurt, which is quite large and its occurrence is highly variable among individuals.

A possible explanation for all seasonal variation in growth in height may be seasonal variation in sunlight which influences the endocrine system and hormones involved in growth regulation.[7] In an experiment testing this hypothesis, one group of boys from Sweden was exposed to sunlamps during the winter while the control group was not, and the results demonstrated that the exposed group averaged 1.5 cm more growth in height than the controls (Nylin, 1929, cited in Bogin[7] and Tanner[11]). However, during the summer, the control group grew faster than the exposed group, resulting in no overall difference in mean annual growth in height. A study of blind children in southern England demonstrated that the months of maximal growth were evenly distributed throughout the year for the blind, while for normally sighted children the months of maximal growth occurred between January and June.[14] The seasonal variation in day length was posited as an explanation for the consolidation of maximal growth into the 6 months for children with normal vision. Marshall[15] tested this hypothesis, examining the growth rates of 300 children on the Orkney Islands in relation to several climatic variables but found low correlations, which he argued does not support the hypothesis that day length is the critical variable.

Two additional studies do, however, support the hypothesis that seasonal variation in sunlight exposure accounts for observed seasonal variation in growth. A study of children in Zaire, Africa,[16] found that the growth in height was more rapid during the dry season than the rainy season. Even though length of day was longer in the rainy season, actual exposure to bright sunlight, or insolation, was greater for the children during the dry season, supporting the role of sunlight in growth regulation.[7] The study by Bogin[13] of children in Guatemala also demonstrated that children 5–7 years old grew faster during the dry versus rainy season and, similar to the African sample, exposure to sunlight was greater during the dry season.

Exposure to sunlight has long been recognized as an important factor for skeletal development. Ultraviolet light stimulates the production of cholecalciferol, vitamin D_3, in human skin; and vitamin D_3 increases intestinal absorption of calcium and regulates the rate of skeletal remodeling and mineralization of new bone tissue.[17] Thus, vitamin D_3 is vitally important for skeletal growth and development, and insufficient exposure to sunlight could impair growth in height. Despite the fortification of milk with vitamin D_2, the major source of vitamin D for humans is the body's synthesis of the D_3 form under stimulation from sunlight.[18] In addition, the marked seasonal variation of vitamin D derivatives in plasma coincide with variation in sunlight; greater sunlight corresponds to the highest levels of the derivatives.[19] Thus, exposure to sunlight and the production of vitamin D_3 may account for the observation that children in temperate climates have a faster rate of growth in height during the spring and summer and that children in the tropics grow more during the dry season, when sunlight exposure is greatest.

The seasonal variation of weight gain can be explained in some populations by seasonal differences in resource availability, nutritional variation and rates of disease, but for other, more well-nourished populations, this explanation is not sufficient.[7] Studies in Guatemala did not find a correlation between weight gain and variation in diet, exercise, or disease.[7] Some have simply suggested that an endogenous seasonal rhythm of weight gain exists in children.[7] Further studies are required to better understand this phenomenon.

There appears also to be seasonal variation in menarche. Studies in Finland observed higher incidences of menarche in spring and summer, and similar seasonal effects were observed in an population from South Africa.[20] This seasonal variation may also be due to variation in light, nutrition, and disease.

HIGH ALTITUDE HYPOXIA

An estimated 140 million people live at high altitude, which is generally defined as greater than 2500 meters (8000 feet).[21] Such environments impose many environmental challenges, which increase as altitude increases.[22] High altitude is a multistressor environment, including in addition to hypoxia, nutritional stress, cold, and radiation (topics discussed elsewhere in this book). At high altitude, the atmosphere contains fewer elemental molecules (oxygen, nitrogen, etc.) per cubic unit of air, although their proportions are the same as at sea level. At high altitude, the partial pressure of oxygen (the air pressure due to the oxygen molecules) in the atmosphere is reduced, which is known as *hypoxia*, and it can lead to hypoxemia, or, insufficient oxygen reaching the tissues. Hypoxia is a unique stressor for humans, because cultural or behavioral adaptations do not overcome it except by exceptional means. The partial pressure of oxygen in the environment affects the amount of hemoglobin in the blood that is saturated with oxygen, which, in turn, affects metabolism, because oxygen is required for normal metabolic activity. Human populations can be found in several high altitude regions globally, including the Andes in South America, the Himalayas in Asia, the high plains of Ethiopia, and the Rocky Mountains in the United States. There is a large variety of biological responses and adaptations to high altitude, and these are reviewed comprehensively in several sources.[21–23] Here we focus on alterations in the pattern of growth and development exhibited by these populations. Both prenatal and postnatal growth and development are distinctly affected by exposure to high altitude; however, whether the effects are solely due to hypoxia or to a combination of hypoxia, nutrition, and other environmental factors should be considered.

A reduction in birth weight at high altitude of approximately 100 g per 1000 m has been well documented,[22] although the exact amount varies, depending on other characteristics of the populations being compared. Mortola et al.[24] reported that from 2000 to 4500 m in Peru, birth weight declined an average of 65 g for every 500 m. Haas et al.[25] observed a mean birth weight of 3415 g at low altitude (400 m) and a mean of 3313 g at high altitude (3600 m) among populations of Amerindian and European heritage in Bolivia, a statistically significant difference. Elsewhere, Haas[26] reported a mean birth weight of 3165 g for Indians at high altitude (3600 m) in Bolivia, and a mean birth weight at low altitude (400 m) of 3427 g for Indian mothers also born at low altitude. At 3100 m in Leadville, Colorado, the mean birth weight was 3126 g but at 1600 m the mean was 3301 g.[27] In addition to birth weight, Haas et al.[25] observed that the crown-heel length of Bolivian newborns in La Paz (3600 m) was 49.0 cm while the mean length at low altitude (400 m) was 49.6 cm, a significant difference.

At high altitude, the entire distribution of birth weights is shifted lower, so that there is also a greater percentage of low birth weight babies (weighing 2500 g or less) born at high altitude. Indeed, the rate at high altitude may reach four times the rate observed at low altitude.[22] In Leadville, Colorado, the frequency of low birth weight ranged from 24 to 45%, averaging 30.8%, while at sea level the frequency was only 10–11%.[28] In Lake County, Colorado, (3000–3350 m) from 1949–1951, 48.3% of births weighed less than 2500 g while for the United States in general for the same period only 7.4% weighed 2500 g or less.[28] The observed increase in low birth weight and the reduction in mean birth weight at high altitude is not due to decreased gestation.[29] The average gestational age is similar for high and low altitude populations, thus it appears instead to be a result of intrauterine growth retardation.[22]

Length of residency of a population may be an important factor mediating the effects of high altitude on birth weight. This is thought to reflect greater genetic adaptation to high altitude among populations of longer residence. Several researchers on the subject have concluded that the longer a population has resided at high altitude, the smaller is the decline in birth weight.[22,23] Populations in the Rocky Mountains have lived at high altitude for the shortest period of time, and they experience the greatest reduction in birth weight relative to sea level inhabitants.[22] Tibetans are generally regarded as having resided at high altitude for the longest. Although exact dates of migration to altitude are still under investigation, they may be as great as 50,000 years, and Tibetans experience the least reduction in birth weight.[22] Andean populations are intermediate for birth weight reduction and may be for length of residency as well.[22] Several studies, however, have reported that human populations in the Andes date back 25,000 years ago or more,[30] so further research is required to substantiate the dates of Tibetan and Andean antiquity. The difference in the rate of low birth weight between high and low altitude also varies among regions, possibly due to length of residency at high altitude. The frequency of low birth weight in the Peruvian Andes at 3400 m is only 10%, which is far lower than the rate at high altitude in Colorado reported by Lichty et al.[28]

At high altitude, the average weight of the placenta can be 10–13% greater than at sea level, and it is more often irregularly shaped.[31,32] However, McClung[33] reported that placental weight was not significantly increased at high altitude but larger in relation to the size of the fetus, owing to the reduction in fetal growth that is common at high altitude.[22,33] The higher birth weights observed among Andean and Tibetan women relative to European and Chinese Han women at high altitude is consistent with the theory that increased oxygen reaches the fetus reducing fetal hypoxic stress in the Andean and Tibetan populations.[21] Two mechanisms by which this can be accomplished are increased ventilation and a placenta that is more vascularized and has greater oxygen-diffusing capacity.[21,22] The Tibetan adaptive strategy for pregnancy at high altitude appears to be to maximize the increase in uterine blood flow rather than arterial oxygen content, while in Andean populations an increased arterial oxygen content maintains sufficient fetal-placental oxygen delivery.[22]

The study of growth at high altitude is one of the few areas in which researchers have sought to measure the adaptive benefit of a particular growth pattern. At low altitude both extremely high and low birth weights are associated with increased morbidity and mortality, and between them is the optimal birth weight, which is associated with the lowest mortality rate. Beall[34] has argued that the optimal birth weight at high altitude is lower than at low altitude and that this decrease is an adaptation to the environment. She examined births at 3860 m and 600 m in Peru and concluded that the optimal birth weight at high altitude was 170 g lower than at low altitude. Others, however, argue that, regardless of the altitude, lower birth weights are detrimental.[22] This issue is not yet resolved.

The pattern of postnatal growth is also altered at high altitude. Experimental animal studies show that weight increases at a slower rate under hypoxic conditions, and microscopic analyses indicate that retarded growth under hypoxic conditions is due to a smaller number of cells, rather than to the reduced cytoplasm observed in growth retardation due to malnutrition.[23] Infants in La Paz were significantly shorter at 1 month old and at 6 months old and the rate of gain in recumbent length was slower at high altitude than low altitude.[35] In Andean studies, a consistent reduction in growth of length and weight from birth to 2 years old exists.[22] Beall et al.[36] reported that low altitude boys from Peru 6–11 years old were 4 kg heavier than their high altitude counterparts and that the weight difference was greater for adolescents 12–18 years old when the low altitude males weighed 11.6 kg more. A similar relationship was observed for females.

Peruvian and Chilean children at high altitude (>4000 m) were significantly shorter than the low altitude children at all ages of childhood and adolescence,[36,37] and the rate of increase in height appears slower at high altitude.[38] This is consistent with the results of a study by Frisancho and Baker[39] in another Andean sample. They observed a delay in growth in height and weight in both sexes, and an extension of the growth period, which reaches 22 years in men and 20 in women.[39] The adolescent growth spurt is delayed in both sexes in the Andes, occurring after 14 years of age in females and 16 years of age in males, and the spurt appears to be less pronounced in males.[39]

The effects of hypoxia on growth at high altitude are difficult to disassociate from the effects of low socioeconomic status and poor nutrition. To avoid this problem, Stinson[40] examined French schoolchildren of middle to upper class who spent varying amounts of time living at high altitude in Bolivia. For both sexes, the French schoolchildren were approximately 6 cm shorter than a reference low altitude U.S. population, demonstrating that high altitude does affect growth independent of socioeconomic status, but the French children were also 13 cm taller than a high altitude Bolivian sample of lower socioeconomic status, indicating low socioeconomic status also reduces growth at high altitude. When the sample was limited to children of Bolivian ancestry to control for genetic effects, only length of residency at high altitude significantly affected height. Children who lived at high altitude for the shortest period of time had an average height that was approximately 3.75 cm taller than the children who spent their entire life at high altitude. Thus, a negative relationship exists between length of residence at high altitude and child growth, where a longer period of residence is associated with smaller children.

This pattern of delayed growth has been observed in other high altitude populations, including the Himalayas and Russian highlands.[23,41] In the high altitude regions (3000 m) in Ethiopia, however, children exhibit a faster rate of growth than in the low altitude regions (1500 m), and the highland children were significantly heavier than lowland children.[42] This observation is unexpected; however, it can be explained by the better nutrition and reduced prevalence of disease at high altitude relative to low altitude in Ethiopia, reminding us that each ecological zone is complex and may contain factors both beneficial and detrimental to growth.

Another characteristic of growth at high altitude is an enlarged chest size and accelerated chest development despite delayed growth and smaller body size (see Figure 8-2).[22,23,43] In a Peruvian sample, high altitude boys and girls of a specific height tended to have statistically significantly larger chest sizes than low altitude children of the same height.[36] Along with chest size, there is an increase in lung volume in high altitude populations.[23,43] This increase may be an adaptation to reduced oxygen availability, since at high altitude, greater lung volumes are associated with increased surface areas that allow for greater gas exchange.[22,23] A high altitude population in the Himalayas in Nepal, however, did not exhibit an increased chest circumference.[41] Children of European ancestry exposed to chronic hypoxia during development also demonstrate increased chest size and lung volumes; however, these traits are smaller than the chest sizes and lung volumes of high altitude natives.[44,45] Also, European children do not seem to exhibit accelerated growth of chest size and lung volumes during childhood and adolescence.[44]

In Andean studies, the heart of the high altitude native is heavier and bigger than that of the low altitude dweller, and studies suggest that this difference is primarily due to lack of involution of the right ventricle.[23] At birth, the morphology of the heart at high and low altitude is similar, but after 3 months of age, the right ventricle at sea level is smaller than the left while at high altitude the right ventricle remains as large or becomes larger.[46] This difference is most marked at the inferior aspect (apex) of the heart.[47] The difference in developmental patterns is explained by the increased work by the right ventricle that pumps against increased

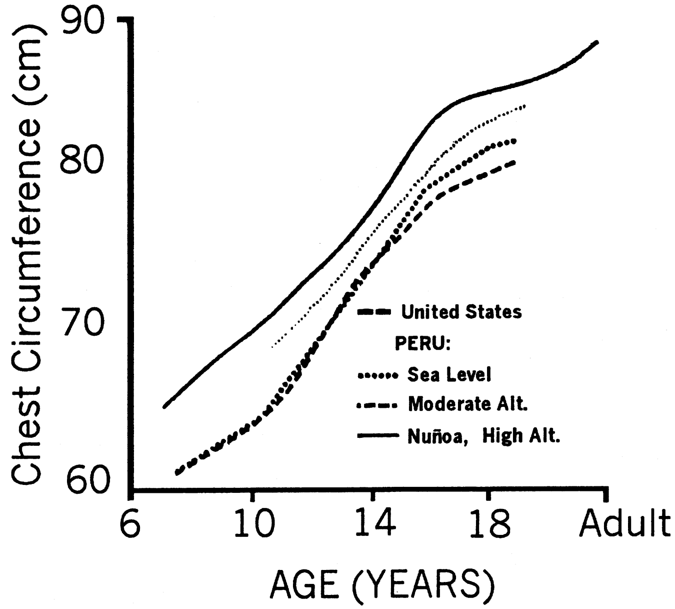

FIGURE 8-2 Comparison of chest circumference among Peruvian children and adults from sea level, moderate altitude, and high altitude. Highland Quechuas from Nuñoa exhibit accelerated growth in chest size. (Source: Frisancho AR, Baker PT. Altitude and growth: A study of the patterns of physical growth of a high altitude Peruvian Quechua population. Amer J Phys Anthropol. 1970;32:279–292. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

pulmonary vascular resistance due to chronic hypoxia.[46] This characteristic of high altitude Andean populations has not been reported for other populations, such as in the Himalayas or Ethiopia.

Skeletal and sexual maturation are also affected by development at high altitude. Skeletal maturation prior to the age of 16 years is retarded in Andean, Himalayan, and Ethiopian high altitude populations relative to U.S. standards.[23,41,42] The average delay in skeletal age is about 20%.[23] After the age of 16, however, the degree of retardation decreases to 10% in the Himalayan and Peruvian samples, and by age 20 years in men and 18 years in women, these populations approach western standards.[23,41] This delay in skeletal maturation parallels the delay in growth and attainment of adult stature in Andean and Himalayan populations. In the Ethiopian samples, both the high and low altitude populations are delayed relative to U.S. standards, which may reflect, in addition to hypoxia, effects of other environmental factors, such as infection and nutrition.

Sexual maturation is also delayed at high altitude; for example, average age at menarche for high altitude girls in Peru was 13.58 years, while it was 12.48 years at sea level.[23] In Bolivia, the median age at menarche in La Paz (3600 m) for girls of European ancestry born and raised at high altitude was 13.1 years and, for those of Aymara ancestry in La Paz, it was 13.4 years.[48] At sea level in Santa Cruz, Bolivia (400 m), the median age of menarche for girls of European ancestry was 12.3 years.[48] For both sexes, the age at which secondary sexual characteristics develop is delayed at high altitude, and adult values of luteinizing hormones in women are attained 1 year later than at sea level.[23] Thus, several indicators of a delayed sexual maturation at high altitude in the Andes exist, and in the Himalayas the reported average age at menarche is 18.1 years,[41] which is quite late. Altitude did not appear to affect sexual development in populations at high altitude in Ethiopia, as these children did not demonstrate a delay in sexual maturation.[42]

Therefore, high altitude appears to have several effects on growth and development, including reduced weight and length at birth, a delay in childhood and adolescent growth, and a delay in skeletal and sexual maturation. Since many of these effects have been observed in controlled experiments with nonhuman animals, they are likely due to hypoxia. However, in human exposure to high altitude, the effect of suboptimal nutrition may add to the reduction and delay in growth, but nutrition would not affect the other aspects of growth patterns (e.g., chest circumference) observed in high altitude populations. Future research may disentangle effects due to different stressors. Growth studies provide some evidence for a genetic adaptation to high altitude; however, this evidence consists of population comparisons showing that the growth deficiency or delay among long-term resident populations is less than the more recently migrated populations. However, specific genes responsible for better adaptation have not been identified.

POLLUTANTS

Pollution is usually defined as unwanted materials (e.g., lead, mercury, particulate matter) or energy (e.g., noise and radiation) produced by human activity or natural processes such as volcanic action. Anthropogenic pollutants are produced from power plants that generate energy, manufacturing industries, transportation, the construction of homes and factories, and even agriculture. Once created, pollutants are dispersed globally to virtually all populations by the dispersion of air and water and through the food chain.

Our knowledge of many pollutants comes from occupational studies, but these mainly concern large, acute exposures to men. Now that we have the technology to accurately measure low levels of toxicants in the environment, we have found them in pregnant women and newborn babies, and we need to understand their effects on the developing organism when environmental insults can have irreparable, long-lasting effects.

The study of human development and toxicants is based on observation without modifying exposures, since an experiment in which exposure is randomized to subjects is obviously unethical. Purely observational studies yield statistical associations and these must be judged in terms of the likelihood that the association is based on biological cause. Five criteria are used for judging the causal basis of statistical associations (see Table 8-1), and studies of growth and pollutants should be designed to meet these criteria as much as possible.

All the listed criteria depend on the accurate and reliable measurement of exposure. The best way to assess exposure is to measure the pollutant of interest in the person or an immediate result of the pollutant in the person. For example, in a study of lead, it is best to measure lead in the blood or bone. An inexpensive but inaccurate method of assessing exposure is the substitution of a measurement made in a geographical zone, such as a postal zone, for the exposure of every child living in the zone. In any zone, people are likely to experience different amounts of true exposure and grouping them together and using an average value leads to misclassification, which then produces large errors in the independent (exposure) variable. Too often studies of growth and pollution are forced for economic reasons to use this latter method, but the effects on growth are more likely to be accurately determined if we can employ the most accurate measures of exposure. Despite difficulty in accurately measuring exposure, there is now considerable evidence that human physical growth and development is sensitive to several pollutants, including lead, the components of air pollution, organic compounds such as polychlorinated biphenyls, as well as some forms of energy such as radiation and noise.

Cigarette Smoking

Cigarette smoke contains a large variety of compounds, including carbon monoxide and cyanide, that can have a variety of detrimental effects on human functioning and growth. These compounds can cross the placenta and affect the fetus, and secondhand cigarette smoke may affect children in households with smokers.[49] Smoking cigarettes before growth is complete (i.e., as a child or adolescent) may also affect growth, but this problem has not been studied sufficiently.

Prenatal growth is very strongly affected by maternal cigarette smoking. Maternal cigarette smoking is the single greatest influence, after gestational age, on birth weight in well-off countries,[50] where nutrition is adequate and cigarette smoking is common. In populations suffering from nutritional stress, very few women smoke during pregnancy, so the effect is minimal or absent. Women who smoke during pregnancy have babies weighing on average 200 g less than babies of nonsmokers,

TABLE 8-1 Criteria for Judging the Causal Basis of Statistical Associations

1. A strong association.
2. Biologic credibility to the hypothesis.
3. Consistency with other studies.
4. Compatible time sequence.
5. Evidence of a dose-response relationship.

and this effect has been replicated in many carefully designed studies. The reduction in birth weight is related to the number of cigarettes smoked. This dose-response relationship is good evidence for a causal relationship between smoking and prenatal growth. Maternal smoking causes reductions of only 2 days or less in gestational length, which cannot account for the birth weight decrement. When birth weights of smokers' and nonsmokers' infants are compared at each week of gestation from weeks 36 through 43, smokers consistently have lower mean birth weights. Just living with a smoker may affect birth weight, as women whose husbands smoked had lower birth weight babies.[51,52]

The reduction in mean birth weight is related to a downward shift of the entire distribution of birth weights. In other words, the 90th weight percentile of smokers' babies is lower than the 90th percentile of the nonsmokers' babies. Similarly, the frequency of LBW (low birth weight, less than 2500 g) is more common among smokers, again irrespective of gestational age, and it is approximately doubled among smokers.

Maternal smoking also is significantly associated with shorter body lengths (about 1 cm), reduced arm circumference, and in some studies, slightly reduced head circumference.[53–56] The sizes of the decrements depend on the amount and timing of cigarette consumption by the mothers in the population. The pattern of reductions may indicate when cigarette smoking begins to depress prenatal growth. Peak weight velocity, including fat deposition, occurs later in the pregnancy than rapid growth of body length and head circumference. Thus, the greatest impact of smoking may be registered in the last trimester of pregnancy. In one longitudinal study using repeated ultrasound imaging, biparietal diameter of the head increased significantly faster among fetuses of nonsmokers from the 28th week of gestation onward; that is, starting near the beginning of the last trimester of pregnancy.

The effect of quitting smoking after conception also informs us of when smoking acts to reduce prenatal growth. Quitting before the fourth month of pregnancy is thought to restore the risk of having a LBW baby to that of a nonsmoker and results in birth weights similar to infants of nonsmokers. Some of this effect is because quitting is more common among light smokers than heavy smokers. When both the amount of smoking and the quitting are considered, very heavy smokers who quit may not fully lower their risk of LBW.[57] However, from a practical point of view, quitting or reducing smoking is advised for all women who smoke and who are or may become pregnant, so strong is the detrimental effect of smoking on the fetus.

In some respects, the stress to the fetus from maternal cigarette smoking resembles the stress of high altitude hypoxia. The primary constituent of tobacco smoke is carbon monoxide. Carbon monoxide, with an affinity for adult hemoglobin 200 times that of oxygen, has an even greater affinity for fetal hemoglobin. It is estimated that if a mother smokes 40 cigarettes per day there is a 10% concentration of carboxyhemoglobin, equivalent to a 60% reduction in blood flow to the fetus. Thus, cigarette smoking exacerbates fetal hypoxia. Given the hypoxic stress, one might expect other adaptations similar to those seen in high altitude populations.

In fact, placenta ratios are larger among smokers, largely due to the reduction in birth weight, but the question of whether placentas of smokers are absolutely larger than those of nonsmokers is not resolved. Some studies have noted that the placentas of heavy smokers are heavier than nonsmokers' placentas,[58,59] a finding consistent with effects seen at high altitude.[31] However, other studies found no difference in placenta size associated with heavy smoking or the nicotine content of cigarettes smoked.[55,60] Smokers' placentas also are thinner, with larger minimum diameters.[58] Some of these changes in placental morphology may be adaptive, given the reduced oxygen-carrying capacity of the blood, but other changes (e.g., calcification) or ones indicative of aging or chronic ischemia (lack of blood flow) in the placenta do not appear to be adaptive.

Cigarette smoke also contains nicotine, which stimulates adrenal production of epinephrine, norepinephrine, and acetylcholine; and this results in less uteroplacental perfusion (blood flow through the uterus and placenta). It also can act on the fetus directly, to increase fetal blood pressure and respiratory rate. In addition, cyanide, lead, and cadmium, all of which are toxic, are contained in cigarette smoke. Cadmium may affect the action of zinc, which is important for growth. Cyanide affects vitamin metabolism and may cause tissue hypoxia and reduced growth as well.[61] Smoking can also affect hormone levels,[62,63] and this in turn could affect prenatal growth.

It is tempting to think that smoking may not act through any of these means, but indirectly by reducing maternal appetite, resulting in reduced ingestion and lower maternal weight gain, but this is not the case. Studies comparing weight gains of smoking and nonsmoking pregnant women found that weight gains are similar. Other studies have controlled for weight gain by matching for weight or through statistical procedures, and the effect of smoking on size at birth is still present.

Postnatal effects of cigarette smoking are less well studied and less clear. Follow-up studies of smokers' offspring have difficulty separating effects that may develop from being exposed to cigarette smoke in utero from the effects of postnatal exposure from living with adult smokers. Ideally, to research the effect of postnatal smoking, one would study children whose mothers did not smoke during pregnancy but who began smoking soon after giving birth. Few mothers meet these conditions, leaving most researchers to study children whose mothers smoked during pregnancy and who have continued to do so after the baby was born. Although some studies have not found lasting effects from birth,[64] many other studies do. The difference may be due to the extent to which other influences on growth are controlled or the size of the sample. Using a sample of a few hundred children, Hardy and Mellits[65] found a 1 cm difference in length at 1 year old that, although small, was statistically significant, but no differences at 4 and 7 years old. In studies using larger samples, differences in height of about 1.5 cm at 3 years old[66] and 5 years old[67] were found. Analysis of the National Child Development Study, which is a very large national sample, detected a deficit of approximately 1 cm in children's heights at 7 and 11 years old associated with maternal smoking.[68] In one study of 3500 adolescents, the heights of 14-year-old girls were reduced by an average of nearly 1 cm, which was statistically significant, but the boys' heights did not differ.[69] However, the National Child Development Study sample found a small but significant reduction at 16 years old in male heights (about 0.9 cm) but not in female heights.[70] It seems that the difference of 1 cm that is present at birth becomes a smaller fraction of the variation in height, which increases as individual differences in the tempo of height growth are expressed and reach their greatest magnitude at puberty.

The effect of passive smoking is small but significant in large samples. Rona and colleagues[71] examined the heights of children in relation to the number of smokers in the household (none, one, or two) and corrected for birth weight to remove effects of maternal smoking during pregnancy. Height declined with more smokers in the home, suggesting that passive smoking may affect postnatal growth.

Adipose tissue growth may also be affected by maternal smoking or by postnatal exposure to second-hand smoke. Schell, Relethford, and Hodges examined 10 anthropometric dimensions of children 6–11 years old in relation to maternal smoking during pregnancy and found significant reductions in measures of adiposity among the offspring of smokers.[72]

This finding is consonant with observations among adults that smokers are leaner[73] and their fat distribution tends to be more centripedal (located on the torso).[74,75] When adult smokers quit smoking, they add fat and attain a more peripheral or gynoid distribution (on the thighs, hips, and arms). This, in turn, is consistent with the observation that cigarette smoking contains antiestrogenic compounds, so that female smokers tend to have fat patterns that resemble those more typical among men. The difference seen in 6- to 11-year-old children may be a late expression of an effect of prenatal exposure or a response to postnatal exposure to cigarette smoke. In either event, adipose differences have not been found at birth.[54,76]

There is no doubt today that cigarette smoking is a powerful cause of reduced prenatal growth. Deficits are greatest in weight at birth, but these appear to be made up during childhood, while the small deficit in length is not. Postnatal exposure to secondhand cigarette smoke seems to reduce height growth slightly, although more replication studies are needed. All studies of growth should consider the effects of smoking carefully, especially if the subject is the growth of the fetus.

Air Pollution

Even though air pollution contains a very heterogeneous category of materials, a number of research studies on the effects of air pollution have been done, and most of these compare two or more settlements that differ in the severity of air pollution. These studies usually report differences in growth that favor the less polluted areas, although not all do.[77] A recent study of 1001 children 9 years old, in Kraków, Poland, found that the growth rates were significantly reduced among children residing in an area with high levels of particulate and sulfur dioxide air pollution compared to children from a reference area with far less air pollution.[78]

The proportion of children classified as having slow growth rates (<10 cm over 2 years) was two to three times higher in the highly polluted area than the low polluted area. Socioeconomic status, as indexed by parental education, did not differ and so was not responsible. An earlier study with a large population of 4- to 12-year-olds also found reduced weight and height in the children from the more polluted region,[79] and another found reduced height in relation to air pollution.[80] Slower skeletal maturation among children from more polluted areas has been observed in several studies.[80,81] In one study of over 10,000 children 7–12 years old, skeletal maturation was delayed significantly in the more air polluted districts.[82] It is possible that air pollution exerts an effect like high altitude hypoxia, limiting the oxygen available for growth. Mikusek[83] found that girls from an air polluted town were delayed in all growth dimensions except chest development, a selective effect similar to the sparing of growth of chest circumference seen in some studies of high altitude Andean children.

The effect of air pollution may begin prenatally. For example, an early study of birth weight in different sections of Los Angeles found that weights decreased in relation to the severity of the air pollution, and the effect was evident after controlling for some of the other large influences on birth weight (mother's cigarette smoking and socioeconomic status). This finding has been replicated in other countries,[84] but there are instances where no effect has been found.[85] The most recent work has tried to determine what components of air pollution may be responsible, the suspended particulate matter or the gases (sulfur oxides, nitrogen oxides, and ozone). A recent study using births in the Czech national birth register in 1991 found that low birth weight was increased in relation to the level of sulfur dioxide air pollution and, to a lesser extent, the level of suspended particulate matter.[86] More studies are needed before we know exactly what components of air pollution are causing reduced growth or whether they all do.

Organic Compounds: Polychlorinated Biphenyls and DDT/DDE

Organic pollutants include many insecticides and herbicides used in agriculture and pest control. DDT was used for controlling malaria-carrying mosquitoes, and its metabolite, DDE, is found in many populations. Polychlorinated biphenyls (PCBs) are a group of 209 compounds that share a basic common structure, and some PCBs are very similar in structure to dioxin, which is thought to be one of the most toxic substances known. PCBs vary in how many chlorine atoms are part of the molecule and where the chlorine atoms are located. These variations influence the fate of the PCB molecule in the environment and its toxicity. Many organic pollutants like PCBs are lipophilic, which means they are stored in fat cells, and they can be retained for years. Lipophilic compounds are concentrated in fat including breast milk and transferred to the fetus and breast-feeding infant. They are also found in dietary items such as fish, meat, and milk products.

PCBs may affect endocrine function, physical growth, maturation, and cognitive or behavioral development of children and youth. Evidence of the effects of

PCBs in humans comes from two types of studies: studies of *acute* poisoning, either food poisoning or an occupational accident, and studies of *chronic* low level exposure, usually from ingestion of foods with slight but measurable contamination.

Ingestion of rice oil contaminated with a mixture of PCBs, dioxin, and dibenzofurans poisoned thousands of adults and children in Japan in 1968 and in Taiwan in 1978–1979, producing diseases called *Yusho* and *Yucheng*, respectively. Yusho/Yucheng infants have had higher rates of mortality and lower body weights at birth.[87] Even children born long after their mothers were exposed to the contaminated oil were more often born prematurely and small at birth,[88] probably because they were exposed to PCBs stored in their mothers' fat tissue. Reduced postnatal growth also characterizes Yusho/Yucheng children. In 1985, the height of children who were exposed in utero was 97% of matched controls and their weight was only 93% of the controls, a statistically significant difference.[87]

Studies of children born to women exposed to smaller amounts of PCBs over a long period of time have also found growth deficits. A common finding is that birth weight is reduced in response to PCB exposure.[89] A study of women working where PCBs were present detected a reduction in the birth weights of their babies amounting to 153 g among women with direct contact with the chemical, and a second follow-up study that controlled more completely for other influences on birth weight found a difference of 114 g.[90,91] The effect was not due to shorter gestations, and both differences were statistically significant. In Sweden, babies of women who consumed fish with higher PCB contamination weighed 80 g less at birth and had smaller head circumferences, differences that are statistically significant.[92] Two studies related reduced birth weight to fetal exposure to dioxin and dioxinlike compounds.[93–95] One longitudinal study of children born to women who consumed PCB-contaminated fish from the American Great Lakes found a substantial difference in birth weight, reduced length, and reduced gestational age; and these reductions increased with each increase in the estimated PCB exposure.[96] However, another longitudinal study of newborns with no source of concentrated exposure showed no effect of PCBs.[97] It is important when interpreting conflicting results such as these to account for differences in exposure among the studies. Certainly, one would expect a smaller effect or none at all when the exposure is very low, and it is difficult to ascertain how exposure levels compare across studies because few of them measure the contaminant compounds in exactly the same way.

The children exposed to PCBs from the Great Lakes fish have been followed, and a significant reduction in their weight was found at 4 years old, although not at 11 years old.[98] The reduction at age 4 was related to the PCB level at birth, reflecting prenatal exposure, but not to their current PCB level. This pattern of association is consistent with the theory that the prenatal period is the critical time for exposure. Two new studies also found a relationship between PCB level and body mass index at puberty, and a reduction in height of nearly 2 cm among children with high levels of DDE, a metabolite of the insecticide DDT.[99,100]

The reduction in growth could be due to interference with hormonal control of growth. Many studies of nonhuman animals have shown that hormone activity can be altered following exposure to PCBs and related compounds. Thyroid hormones are especially important for normal physical and mental growth and development. In one study, TSH (thyroid-stimulating hormone) levels in the neonate were elevated with higher levels of PCBs and related compounds in the neonate.[101] Elevated TSH is an indication that circulating levels of thyroid hormones are too low. After infancy, the relationship of PCBs to TSH was no longer present, but the damage may have already been done. Effects on important aspects of prenatal development, such as brain development, may last long after the most obvious effects are gone and arise long after infancy. Many types of PCB molecules structurally resemble thyroid hormones and some sex steroids, and the similarity may confuse the body, producing slightly deranged hormonal messages. This is a highly controversial area of research and the complete picture is not clear at this time, although some pieces of the picture are tantalizing. Preliminary results, from the follow-up of Yucheng boys 11–14 years old, found significantly reduced penile lengths a possible effect of their exposure prenatally when critical sexual differentiation and development is occurring.[102]

There is sufficient evidence to be concerned about PCB exposure in children and the fetus. Especially convincing are the controlled laboratory studies of higher primates and rodents that show reductions in growth and alterations in sexual development dependent on normally functioning hormonal systems. Although we do not know whether a low level exposure will produce effects on child development, we see that high exposures, such as those from food heavily contaminated with PCBs, can produce predictable effects, and the possibility that the fetus is especially sensitive PCBs, even at low levels, remains a very viable hypothesis.

Lead

Lead has been a common pollutant since it was first added to paint and gasoline. In countries where leaded paint is absent, lead is less of a problem for children. In the United States, lead burdens are higher among urban, disadvantaged, minority children because of their proximity to dilapidated housing with flaking leaded paint and to roadways. In the late 1970s, one in six African-American children from the central sections of large cities had lead levels that exceeded 25 μg/dl, which was the definition of lead poisoning at the time. More recent surveys show that average lead levels have decreased among U.S. children nationwide, but the poor, inner city children do not share equally in this decrease. During this period of declining lead levels, we also learned that even low levels of lead can be detrimental to human health and functioning.

Studies often indicated that at birth growth is reduced and gestations are shorter with increased lead exposure,[103,104] although some studies do not detect such differences.[105] The reasons for the inconsistency have not been determined. One large, careful study of poor mothers and their newborns in Cincinnati, Ohio, found a reduction in birth weight of nearly 200 g in relation to the log of maternal blood lead level.[106] Another study in Albany, New York, found similar effects on birth weight and a reduction in skinfolds.[107] In both studies birth length was less affected than birth weight, and head circumference was not affected at all.

The effect of pollutants on birth weight has been studied largely because birth weight is routinely collected as part of public health surveillance, but only a few investigators have studied growth among lead-exposed children. The three largest studies used national survey data from the United States. Data from the second National Health and Nutrition Examination survey data (1976–1980), involving about 7000 children less than 7 years old, showed that lead level was negatively related to stature, weight, and chest circumference after controlling for other important influences on growth.[108] Compared to children with a blood lead level of 0, heights of children with the mean lead level were 1.5% shorter at the mean age of 59 months. The second large study used a data set of 7–12-year-old children from the Hispanic Health and Nutrition Examination Survey (1982–1984). Children whose blood lead levels were above the median for their age and sex, were 1.2 cm shorter than those with lead below the median.[109] The third study, using anthropometric data from the Third National Health and Nutrition Examination Survey (1988–1994) for non-Hispanic children 1–7 years old, found statistically significant reductions of 1.57 cm in stature and 0.52 cm in head circumference for each 10 μg of lead in the blood.[110] Studies with smaller samples also found growth decrements in height, weight, and head circumference of similar magnitude, indicating that the associations of growth and lead reported for national samples of U.S. children may be present elsewhere.[111,112] Finally, other anthropometric dimensions may also be decreased.[113]

These studies are cross-sectional, that is, lead and stature were measured simultaneously, and consequently one could argue (and some have) that short children are simply exposed to more lead rather than lead reduces child growth. However, experimental studies of nonhuman animals show very clearly that growth is reduced following lead exposure, which supports the latter explanation. On the other hand, lead doses tend to be high in experiments with laboratory animals, and the question about the effects of low doses on humans remains. Few longitudinal studies have been made of lead and growth. In the Cincinnati study, infants born to mothers with prenatal lead levels above the sample average and whose lead level changed over the interval of 3–15 months of age, grew less over that period.[114–116] Similarly, when the children reached 33 months of age, two groups of children had decreased stature: those with low lead levels prenatally but high lead levels from 3 to 15 months and the children with high lead levels in the prenatal *and* postnatal period. Low lead levels and decreasing lead levels were not related to growth measures.

Another study involved young adults who contributed deciduous teeth at 6 or 7 years of age for analysis of lead content.[117] The tooth lead level was compared to their weight and height at age 20, and a significant positive relationship with body mass index was evident but not with weight or height alone. These results are not consistent with those from the study of Cincinnati children, and the possibility that nutrition is playing a role cannot be excluded. Although small effects of pollutants on growth signal toxicity, small effects are also difficult to observe accurately, due to normal variation in diet, cigarette smoking, and other factors.

Therefore, before reaching a firm conclusion, more carefully designed research on this subject is required.

For example, one study of over 8000 girls from Poland found that girls in towns with more lead had earlier ages at menarche.[118] The finding is unexpected, since higher lead levels have been associated with poorer growth of height and weight, not faster growth (see earlier). In this study, girls were assigned to exposure groups according to the level of lead in their environment, so lead was not measured directly in individuals. Thus, girls with different blood lead levels may have been grouped together. Although pollution and urban dwelling often coincide, and urban dwelling is often associated with earlier menarche, in this study urban social factors may not be responsible for the results, since social factors were well controlled in the study design and analysis. At this time, a mechanism for the effect of lead on sexual maturation is not known. Further studies into toxicants and sexual maturation are warranted to confirm this finding and elucidate the mechanism that produces the effect. In general, it is prudent to separate effects on maturation from effects on growth, because the mechanisms for their effects may be different.

Research on the biological mechanism for the effect of lead on growth has been done. Growth velocity can increase when children receive chelation therapy to remove lead from the body.[119] When children's lead levels have been reduced, their stimulated peak human growth hormone levels are significantly higher than when lead levels are at a toxic level. In addition, among children with high levels of lead, IGF-1 is reduced with increasing lead level. These results help make the statistical associations between lead and reduced height growth more understandable as true biological effects.

A truism in toxicology is that the dose makes the poison. This seems true enough in the case of lead. Very high levels are related to growth and the hormones related to growth. Lower doses have also been seen to produce effects, although the size of the effect is far lower and most easily detected in studies with large samples, such as population studies.

Radiation

Radiation is an energy that exists in several forms, some of which can be extremely damaging to cells. Judging past exposure is difficult and based on life history reports of possible exposures to mundane sources (i.e., medical X rays, airplane flights), which can be inaccurate. Little work has been done on growth in relation to mundane sources of radiation. One study did find that women who had been exposed prenatally to medical X rays were about 1.5 times more likely to experience menarche before the age of 10 years,[120] and others have detected postnatal growth retardation.[121] Most work on radiation concerns persons exposed to radiation from devastating atomic bomb attacks or tests. In these studies, dose can be estimated by determining location vis-à-vis the epicenter of the blast. Several studies have found that in utero exposure to an atomic bomb blast is associated with reduced head circumference, height, and weight during childhood and adolescence and that the reduction is related to an estimated dose.[121,122] One study of accidental exposure to a bomb test found that early postnatal exposure is detrimental as well.[123] In these early studies, maturation rate, if examined at all, was not affected significantly. The most recent work on growth and radiation examined growth at adolescence among survivors of Hiroshima and Nagasaki atomic bombs.[124] From 10–18 years old, total in utero exposure was related to a reduction of several centimeters in stature, but it was not possible to see whether exposure in a particular trimester was especially damaging. There was no test of an effect on maturation.

Noise

Studies of noise are hampered by difficulty measuring a child's past exposure to noise. It is usually estimated by distance from a powerful noise source, such as an airport. Other sources of noise are assumed to be random and therefore do not bias the results. The quality of the study varies in terms of the accuracy of noise exposure measurement and the degree to which other influences on growth are controlled. Several studies examined prenatal growth in relation to maternal exposure to noise from the workplace and found small effects or none at all.[125–127] Studies of airports, where noise stress may be more severe or better measured, found fairly consistently that birth weight is depressed in relation to exposure.[128–134] Unfortunately, each study uses a different metric for measuring noise, making it impossible to compare the amount of reduction among studies. Schell compared births to women residing near an airport who were exposed to noise levels of 100 decibels (dBA) or more to births to women exposed to less airplane noise and observed a difference of 316 g among female infants, an extremely large amount.[130] Similarly, Knipschild, Meijer, and Sallé[134] found a significant reduction in birth weight among females but not males. Other studies have not examined effects by sex, but further research might determine whether effects of noise stress is modified by gender. In addition, whether noise stress or some other factor produces the associations is of some concern. Large sample studies that looked for a dose-response relationship by comparing several groups differing in exposure found that maternal noise exposure is negatively related to birth weight in a fairly consistent manner (see Figure 8-3).[133] Examining the rate of low birth weight and the rate of jet airplane flyovers at Kobe airport when jets were first introduced provides further evidence for a causal effect of noise stress. Prior to the introduction of jets, the rate of low birth weight was lower near the airport than in the rest of Japan, but as soon as jet flights began, the rate of low birth weight increased markedly and the increase continued to parallel the increased number of jet takeoffs. The temporal association strongly suggests that the jet takeoffs are causally related to the change in the frequency of low birth weight.

Studies of postnatal growth are very few, perhaps owing to the difficulty of estimating noise exposure for postnatal life. The first such study found reduced heights and weights among the children exposed to high noise from an airport in Japan.[135]

More recent studies found a reduction in height at 3 years old (see Figure 8-4) and a reduction in soft-tissue dimensions in children 5–12 years old.[136]

An effect of noise seems plausible, based on what we know about the relationship of high noise to the stress response and the relationship between stress and growth.

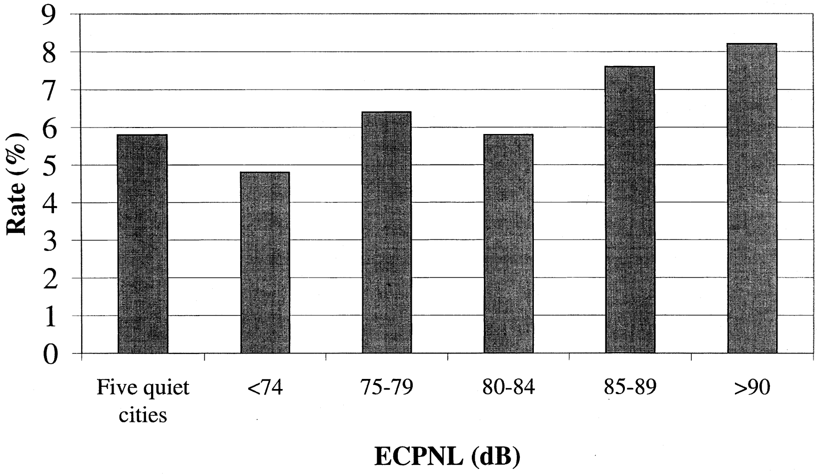

FIGURE 8-3 Percentage of low birth weight infants (<2500 g) in 1969 according to mothers' exposure to aircraft noise measured in equivalent continuous perceived noise levels (ECPNL) (dB). (Source: Adapted from Ando and Hattori.[133])

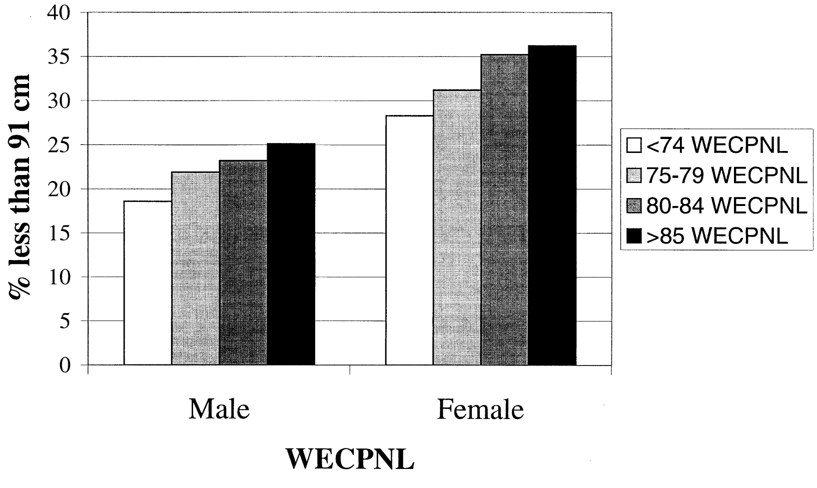

FIGURE 8-4 Percentage of 3-year-old children <91 cm tall by noise exposure measured in weighted equivalent continuous perceived noise levels (WECPNL). (Source: Adapted from Schell and Ando.[137])

Noise is a classic physiological stressor, as it activates the hypothalamic-pituitary-adrenal axis in the same way as other stressors (see Figure 8-5). Noise stress stimulates the autonomic nervous system, which stimulates the adrenal medulla to produce epinephrine and norepinephrine. It also stimulates the pituitary gland, which in turn affects the adrenal cortex, the thyroid, and the gonads. Corticosteroids produced by the adrenal cortex affect growth directly. The thyroid gland regulates metabolism, and its hormones are essential for normal growth and development. Influences on gonadal functioning can influence growth and maturation. Thus, an effect of noise on growth is biologically plausible and seems evident in the studies just reviewed. Since noise is a form of stress, studying noise exposure is a way of learning about the effects of other kinds of stress as well.

One general observation is that the effects of any pollutant depend on the dose. Effects of noise are not present in any study unless the exposures are quite high,

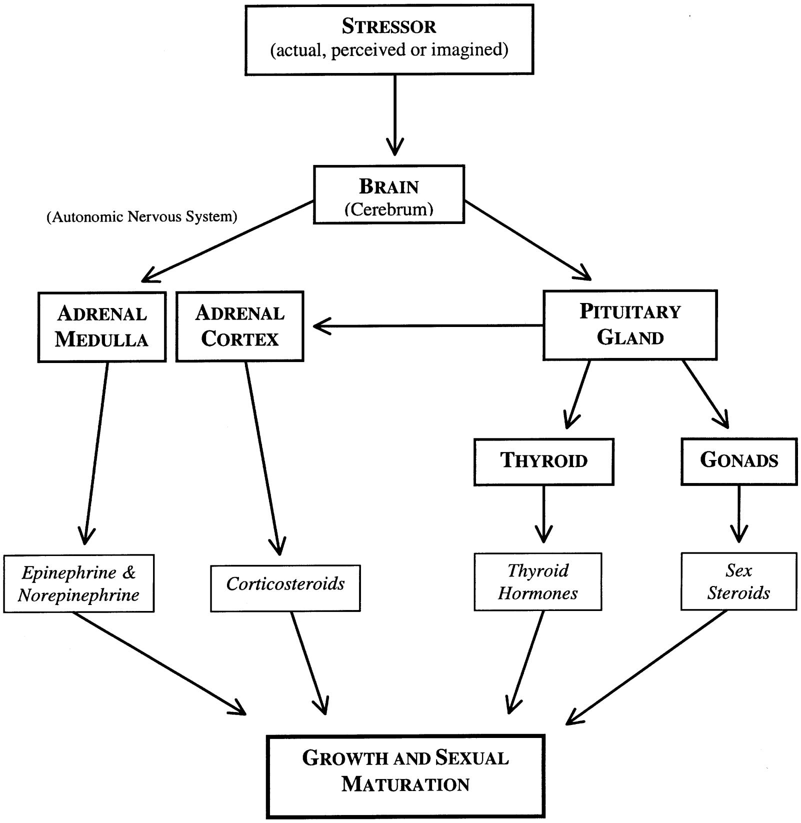
STRESSOR
(actual, perceived or imagined)
BRAIN
(Cerebrum)
(Autonomic Nervous System)
ADRENAL MEDULLA
ADRENAL CORTEX
PITUITARY GLAND
THYROID
GONADS
Epinephrine & Norepinephrine
Corticosteroids
Thyroid Hormones
Sex Steroids
GROWTH AND SEXUAL MATURATION

FIGURE 8-5 The biological stress response.

perhaps over 100 dBA. Statements summarizing the relationship between noise and growth have to be careful about specifying the range of exposure observed. The absence of an effect within a range of low noises does not mean there is no effect at higher levels. In general, statements about the relationship between any environmental factor, whether it is altitude or noise, should refer only to the ranges of exposures observed and should not extrapolate results to exposures above or below that range, otherwise results among studies will appear more inconsistent than they really are.

HOW DO WE INTERPRET DIFFERENCES IN GROWTH RELATED TO ENVIRONMENTAL FACTORS?

Recalling the two interpretations of growth reduction reviewed at the chapter's outset, it seems that the interpretation used depends on the environmental factor considered: Slow and/or reduced growth is a disadvantage created by adverse health conditions (this is the growth monitoring or "biomedical" model), or slow and/or reduced growth is an adaptive response (i.e., beneficial) to features of the environment (the adaptation model). While no covering law dictates which interpretation is appropriate in which circumstances, in general, it seems that growth reductions related to anthropogenic factors (lack of material resources for the child, including poor medical care and poor nutrition) tend to be interpreted with the growth as a monitor model, while growth reduction related to features of the physical environment tend to be interpreted in an adaptive framework. This simple distinction is not foolproof. Air pollution, an anthropogenic factor, is also a product of volcanoes and other natural processes. Ultimately, the view that growth reduction has adaptive benefits for the individual (affecting reproduction or functioning such as cognition) will be determined by studies that seek to measure the adaptive benefits. This future work will determine whether the view of growth as adaptive is truly justified.

CONCLUSION

In addition to effects of nutrition and socioeconomic factors, the immediate physical environment can affect human physical growth and development. This conclusion is supported by many of the studies reviewed here on altitude, temperature, and climate. Studies of pollutants also show effects on growth, although many of these studies have flaws that come from valued and important limitations on experiments with people. However, the results from numerous, carefully executed studies of nonhuman animals support the studies on humans. When compared to the effect of malnutrition, the effect of pollutants can seem small, but the size of the effect depends on the extent of exposure to the pollutant. Thus, cigarette smoking exerts a large or small effect in a population depending on how prevalent smoking is in that population. If we clean up the environment, child growth will be little affected by air pollution, but if children grow up in an environment with many types of pollution, the effect of all the pollutants together may be large. Indeed, studies show that in industrialized countries the poor children have more exposure to pollutants, and the result can be impaired growth. It is wise to remember that exposure to many of the pollutants that affect growth are mediated by social factors, as is nutritional deprivation. Thus, growth can be considered as a monitor of the general quality of children's environments.

REFERENCES

1. Lasker GW. Human biological adaptability. Science. 1969;166:1480–1486.
2. Schell LM. Human biological adaptability with special emphasis on plasticity: History, development and problems for future research. In: Mascie-Taylor CG, Bogin B (eds). Human Variability and Plasticity. Cambridge: Cambridge University Press, 1995:213–237.
3. Huss-Ashmore R. Theory in human biology: Evolution, ecology, adaptability, and variation. In: Stinson S, Bogin B, Huss-Ashmore R, O'Rourke D (eds). Human Biology: An Evolutionary and Biocultural Perspective. New York: Wiley, 2000:1–25.
4. Ulijaszek SJ, Huss-Ashmore R. Human Adaptability: Past, Present, and Future. Oxford: Oxford University Press, 1997:1–325.
5. Roberts DF. Climate and Human Variability. Menlo Park, CA: Cummings Publishing Company, 1978.
6. Newman MT. The application of ecological rules to the racial anthropology of the aboriginal New World. Amer Anthropol. 1953;55:311–327.
7. Bogin B. Patterns of Human Growth. Cambridge: Cambridge University Press, 1988.
8. Malina RM, Bouchard C. Growth, Maturation, and Physical Activity. Champaign, IL: Human Kinetics Books, 1991.
9. Eveleth PB. The effects of climate on growth. Ann NY Acad Sci. 1966;134:750–759.
10. Palmer CE. Seasonal variation of average growth in weight of elementary school children. Pub Health Rep. 1933;48:211–233.
11. Tanner JM. Growth at Adolescence. Oxford: Blackwell Science, 1962.
12. Bogin B. Monthly changes in the gain and loss of growth in weight of children living in Guatemala. Am J Phys Anthropol. 1979;51:287–292.
13. Bogin B. Seasonal pattern in the rate of growth in height of children living in Guatemala. Am J Phys Anthropol. 1978;49:205–210.
14. Marshall WA, Swan AV. Seasonal variation in growth rates of normal and blind children. Hum Biol. 1971;43:502–516.
15. Marshall WA. The relationship of variations in children's growth rates to seasonal climatic variations. Ann Hum Biol. 1975;2:243–250.
16. Vincent M, Dierickx J. Etude sur la croissance saisonnière des écoliers de Léopoldville. Annales de la Societé Belge de Médecine Tropicale. 1960;40:837–844.
17. Griffin JE, Ojeda SR. Textbook of Endocrine Physiology. Oxford: Oxford University Press, 1996.
18. Haddad JG, Hahn TJ. Natural and synthetic sources of circulating 25-hydroxyvitamin D in man. Nature. 1973;244:515–517.
19. Stamp TCB, Round JM. Seasonal changes in human plasma levels of 25-hydroxyvitamin D. Nature. 1974;247:563–565.
20. Johnston FE. Control of age at menarche. Hum Biol. 1974;46:159–171.
21. Beall CM, Steegman Jr. AT. Human adaptation to climate: Temperature, ultraviolet radiation, and altitude. In: Stinson S, Bogin B, Huss-Ashmore R, O'Rourke D (eds). Human Biology: An Evolutionary and Biocultural Perspective. New York: Wiley, 2000:163–224.

22. Moore LG, Niermeyer S, Zamudio S. Human adaptation to high altitude: Regional and life-cycle perspectives. Yearb Phys Anthropol. 1998;41:25–64.
23. Frisancho AR. Human Adaptation and Accommodation. Ann Arbor: University of Michigan Press, 1993.
24. Mortola JP, Frappell PB, Aguero L, Armstrong K. Birth weight and altitude: A study in Peruvian communities. J Pediat. 2000;136:324–329.
25. Haas JD, Frongillo EA, Stepick CD, Beard JL, Hurtado LG. Altitude, ethnic and sex difference in birth weight and length in Bolivia. Hum Biol. 1980;52:459–477.
26. Haas JD. Maternal adaptation and fetal growth at high altitude in Bolivia. In: Greene LS, Johnston FE (eds). Social and Biological Predictors of Nutritional Status, Physical Growth and Neurological Development. New York: Academic Press, 1980:257–290.
27. Leibson C, Brown M, Thibodeau S, Stevenson D, Vreman H, Cohen R, et al. Neonatal hyperbilirubinemia at high altitude. Amer J Dis Child. 1989;143:983–987.
28. Lichty JA, Ting RY, Bruns PD, Dyar E. Studies of babies born at high altitude. Part I. Relation of altitude to birth weight. Amer J Dis Child. 1957;93:666–669.
29. Haas JD. Prenatal and infant growth and development. In: Baker PT, Little MA (eds). Man in the Andes. Stroudsburg, PA: Dowden, Hutchinson & Ross, 1976:161–179.
30. Lynch TF. Glacial-age man in South America? A critical review. Amer Antiq. 1990;55:12–36.
31. Kruger H, Arias-Stella J. The placenta and the newborn infant at high altitudes. Amer J Obstet Gynecol. 1970;106:586–591.
32. Chabes A, Pereda J, Hyams L, Barrientos N, Perez J, Campos L, et al. Comparative morphometry of the human placenta at high altitude and at sea level. Obstet Gynecol. 1967;31:178–-185.
33. McClung J. Effects of High Altitude on Human Birth. Cambridge, MA: Harvard University Press, 1969.
34. Beall CM. Optimal birthweights in Peruvian populations at high and low altitudes. Am J Phys Anthropol. 1981;56:209–216.
35. Haas JD, Moreno-Black G, Fongillo Jr. EA, Pabon JA, Pareja GL, Ybarnegaray JU, et al. Altitude and infant growth in Bolivia: A longitudinal study. Am J Phys Anthropol. 1982;59:251–262.
36. Beall CM, Baker PT, Baker TS, Haas JD. The effects of high altitude on adolescent growth in southern Peruvian Amerindians. Hum Biol. 1977;49:109–124.
37. Mueller WH, Yen F, Rothhammer F, Schull WJ. A multinational Andean genetic and health program. VI. Physiological measurements of lung function in an hypoxic environment. Hum Biol. 1978;50:489–513.
38. Hoff C. Altitudinal variation in the physical growth and development of Peruvian Quechua. Homo. 1974;24:87–99.
39. Frisancho AR, Baker PT. Altitude and growth: A study of the patterns of physical growth of a high altitude Peruvian Quechua population. Am J Phys Anthropol. 1970;32:279–292.
40. Stinson S. The effect of high altitude on the growth of children of high socioeconomic status in Bolivia. Am J Phys Anthropol. 1982;59:61–71.
41. Pawson IG. Growth characteristics of populations of Tibetan origin in Nepal. Am J Phys Anthropol. 1977;47:473–482.
42. Clegg EJ, Pawson IG, Ashton EH, Flinn RM. The growth of children at different altitudes in Ethiopia. Philos Trans Royal Soc London. 1972;264:403–437.
43. Hurtado A. Respiratory adaptation in the Indian Natives of the Peruvian Andes. Studies at high altitude. Am J Phys Anthropol. 1932;17:137–165.
44. Greksa LP, Beall CM. Development of chest size and lung function at high altitude. In: Little MA, Haas JD (eds). Human Population Biology: A Transdisciplinary Science. New York: Oxford University Press, 1989:222–238.
45. Brutsaert TD, Soria R, Caceres E, Spielvogel H, Haas JD. Effect of developmental and ancestral high altitude exposure on chest morphology and pulmonary function in Andean and European/North American natives. Amer J Hum Biol. 1999;11:383–395.
46. Penaloza D, Arias-Stella J, Sime F, Recavarren S, Marticorena E. The heart and pulmonary circulation in children at high altitudes. Pediatr. 1964;34:568–582.

47. Recavarren S, Arias-Stella J. Topography of right ventricular hypertrophy in children native to high altitude. Amer J Pathol. 1962;41:467–475.
48. Greksa LP. Age of menarche in Bolivian girls of European and Aymara ancestry. Ann Hum Biol. 1990;17:49–53.
49. Misra DP, Nguyen RHN. Environmental tobacco smoke and low birth weight: a hazard in the workplace. Environ Health Perspect. 2000;107:897–904.
50. Kramer MS. Intrauterine growth and gestational duration determinants. Pediatr. 1987;80:502–511.
51. Mathai M, Vijayasri R, Babu S, Jeyaseelan L. Passive maternal smoking and birthweight in a South Indian population. Brit J Obstet Gynaecol. 1992;99:342–343.
52. Borlee I, Bouckaert A, Lechat MF, Misson CB. Smoking patterns during and before pregnancy. Euro J Obstet Gynecol Reprod Biol. 1978;8:171–177.
53. Schell LM, Hodges DC. Variation in size at birth and cigarette smoking during pregnancy. Am J Phys Anthropol. 1985;68:549–554.
54. Harrison GG, Branson RS, Vaucher YE. Association of maternal smoking with body composition of the newborn. AJCNA. 1983;38:757–762.
55. Olsen J. Cigarette smoking in pregnancy and fetal growth. Does the type of tobacco play a role? Int J Epidemiol. 1992;21:279–284.
56. Haste FM, Anderson HR, Brooke O, Bland JM, Peacock J. The effects of smoking and drinking on the anthropometric measurements of neonates. Paediatr Perinatal Epidemiol. 1991;5:83–92.
57. Schell LM, Relethford JH, Madan M, Naamon PBN, Hook EB. Unequal adaptive value of changing cigarette use during pregnancy for heavy, moderate, and light smokers. Amer J Hum Biol. 1994;6:25–32.
58. Christianson RE. Gross differences observed in the placentas of smokers and nonsmokers. Amer J Epidemiol. 1979;110:178–187.
59. Naeye RL. Effects of maternal cigarette smoking on the fetus and placenta. Brit J Obstet Gynaecol. 1978;85:732–737.
60. Mulcahy R, Murphy J, Martin F. Placental changes and maternal weight in smoking and nonsmoking mothers. Amer J Obstet Gynecol. 1970;106:703–704.
61. Andrews J. Thiocyanate and smoking in pregnancy. J Obstet Gynecol Brit Commonwealth. 1973;80:810–814.
62. Field AE, Colditz GA, Willett WC, Longcope C, McKinlay JB. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab. 1994;79:1310–1316.
63. Bremme K, Lagerström M, Andersson O, Johansson S, Eneroth P. Influences of maternal smoking and fetal sex on maternal serum oestriol, prolactin, hCG, and hPL levels. Arch Gynecol Obstet. 1990;247:95–103.
64. Conter V, Cortinovis I, Rogari P, Riva L. Weight growth in infants born to mothers who smoked during pregnancy. Brit Med J. 1995;310:768–776.
65. Hardy JB, Mellits ED. Does maternal smoking during pregnancy have a long-term effect on the child? Lancet. 1972;2:1332–1336.
66. Fox NL, Sexton M, Hebel JR. Prenatal exposure to tobacco. I. Effects on physical growth at age 3. Int J Epidemiol. 1990;19:66–71.
67. Wingerd J, Schoen EJ. Factors influencing length at birth and height at 5 years. Pediatr. 1974;53:737–741.
68. Butler NR, Goldstein H. Smoking in pregnancy and subsequent child development. Brit Med J. 1973;4:573–575.
69. Rantakallio P. A follow up to the age of 14 of children whose mothers smoked during pregnancy. Acta Paediatr Scand. 1983;72:747–753.
70. Fogelman K. Smoking in pregnancy and subsequent development of the child. Child: Care, Health Devel. 1980;6:233–249.
71. Rona RJ, Florey CdV, Clarke GC, Chinn S. Parental smoking at home and height of children. Brit Med J. 1981;283:1363.

72. Schell LM, Relethford JH, Hodges DC. Cigarette use during pregnancy and anthropometry of offspring 6–11 years of age. Hum Biol. 1986;58:407–420.
73. Goldbourt U, Medalie JH. Characteristics of smokers, non-smokers and ex-smokers among 10,000 adult males in Israel. Amer J Endriocrinol. 1977;105:75–86.
74. Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. JAMA. 1989;261:1169–1173.
75. Troisi RJ, Heinhold JW, Vokonas PS, Weiss ST. Cigarette smoking, dietary intake, and physical activity; effects on body composition—the Normative Aging Study. AJCNA. 1991;53:1104–1111.
76. D'Souza SW, Black P, Richards B. Smoking in pregnancy: associations with skinfold thickness, maternal weight gain, and fetal size at birth. Brit Med J. 1981;282:1661–1663.
77. Danker-Hopfe H, Drobna M, Cermakova Z. Air pollution and growth of 3- to 7-year-old children from Bratislava. (GENERIC) Ref Type: Report, Soshowiec, Poland, 1996.
78. Jedrychowski W, Flak E, Mroz E. The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. Environ Health Perspect. 1999;107:669–674.
79. Antal A, Timaru J, Muncaci E, Ardevan E, Ionescu A, Sandulache L. Les variations de la reactivite de l'organisme et de l'etat de sante des enfants en rapport avec la pollution de l'air communal. Atmos Environ. 1968;2:383–392.
80. Thielebeule U, Pelech L, Grosser P-J, Horn K. Body height and bone age of schoolchildren in areas of different air pollution concentration. Z Ges Hyg. 1980;26:771–774.
81. Schlipköter HW, Rosicky B, Dolgner R, Peluch L. Growth and bone maturation in children from two regions of the F.R.G. differing in the degree of air pollution: Results of the 1974 and 1984 surveys. J Hyg Epidemiol Microbiol Immunol. 1986;30:353–358.
82. Schmidt P, Dolgner R. Interpretation of some results of studies in schoolchildren living in areas with different levels of air pollution. Zbl Bakt Hyg I Abt Orig. 1977;165:539–547.
83. Mikusek J. Developmental age and growth of girls from regions with high atmospheric air pollution in Silesia. Roczniki Panstwowego Zakludu Higieny. 1976;27:473–481.
84. Nordström S, Beckman L, Nordenson I. Occupational and environmental risks in and around a smelter in northern Sweden. I. Variations in birth weight. Hereditas. 1978;88:43–46.
85. Dolk H, Pattenden S, Vrijheid M, Thakrar B, Armstrong B. Perinatal and infant mortality and low birth weight among residents near cokeworks in Great Britain. Arch Envir Health. 2000;55:26–30.
86. Bobak M. Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect. 2000;108:173–176.
87. Rogan WJ, Gladen BC, Hung K-L, Koong S-L, Shih L-Y, Taylor JS, et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science. 1988;241:334–336.
88. Yen YY, Lan SJ, Yang CY, Wang HH, Chen CN, Hsieh CC. Follow-up study of intrauterine growth of transplacental Yu-Cheng babies in Taiwan. Bull Environ Contam Toxicol. 1994;53:633–641.
89. Schell LM. Effects of pollutants on human prenatal and postnatal growth: Noise, lead, polychlorinated compounds and toxic wastes. Yearb Phys Anthropol. 1991;34:157–188.
90. Taylor PR, Stelma JM, Lawrence CE. The relation of polychlorinated biphenyls to birth weight and gestational age in the offspring of occupationally exposed mothers. Amer J Epidemiol. 1989;129:395–406.
91. Taylor PR, Lawrence CE, Hwang H-L, Paulson AS. Polychlorinated biphenyls: Influence on birthweight and gestation. Amer J Pub Health. 1984;74:1153–1154.
92. Rylander L, Strömberg U, Dyremark E, Östman C, Nilsson-Ehle P, Hagmar L. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. Amer J Epidemiol. 1998;147:493–502.
93. Patandin S, Koopman-Esseboom C, Weisglas-Kuperus N, Sauer PJJ. Birth weight and growth in Dutch newborns exposed to background levels of PCBs and dioxins. Organohalogen Compounds. 1997;34:447–450.
94. Patandin S, Koopman-Esseboom C, De Ridder MAJ, Weisglas-Kuperus N, Sauer PJJ. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res. 1998;44:538–545.

95. Vartiainen T, Jaakkola JJK, Saarikoski S, Tuomisto J. Birth weight and sex of children and the correlation to the body burden of PCDDs/PCDFs and PCBs of the mother. Environ Health Perspect. 1998;106:61–66.
96. Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age. J Pediatr. 1984;105:315–320.
97. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J, et al. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr. 1986;109:335–341.
98. Jacobson JL, Jacobson SW, Humphrey HEB. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol. 1990;12:319–326.
99. Gallo MV, Ravenscroft J, Denham M, Schell LM, DeCaprio A. The Akwesasne Task Force on the environment. Environmental contaminants and growth of Mohawk adolescents at Akwesasne. In: Gilli G, Schell LM, Benso L (eds). Human Growth from Conception to Maturity. London: Smith-Gordon, in press.
100. Longnecker MP, Klebanoff MA, Brock J, Zhou H, Daniels JL. Background-level in utero exposure to the ubiquitous DDT metabolite DDE is associated with reduced height at age 7 years. Acta Med Auxol. 2000;32:73.
101. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, LutkeSchipholt IJ, Van Der Paauw CG, Tuinstra LGMT, et al. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr Res. 1994;36:468–473.
102. Guo YL, Lambert GH, Hsu C-C. Growth abnormalities in the population exposed *in utero* and early postnatally to polychlorinated biphenyls and dibenzofurans. Environ Health Perspect. 1995;103:117–122.
103. Schell LM. Pollution and human growth: Lead, noise, polychlorobiphenyl compounds and toxic wastes. In: Mascie-Taylor CG, Lasker GW (eds). Applications of Biological Anthropology to Human Affairs. Cambridge: Cambridge University Press, 1991:83–116.
104. Pietrzyk JJ, Nowak A, Mitkowska Z, Zachwieja Z, Chlopicka J, Krosniak M, et al. Prenatal lead exposure and the pregnancy outcome. A case-control study in Southern Poland. Przeglad Lekarski. 1996;53:342–347.
105. Andrews KW, Savitz DA, Hertz-Picciotto I. Prenatal lead exposure in relation to gestational age and birth weight: A review of epidemiologic studies. Amer J Indust Med. 1994;26:13–32.
106. Bornschein RL, Grote J, Mitchell T, Succop PA, Dietrich KN, Krafft K, et al. Effects of prenatal lead exposure on infant size at birth. In: Smith MA, Grant L, Sors AI (eds). Lead Exposure and Child Development. Dordrecht: Kluwer, 1988:307–319.
107. Schell LM, Stark AD. Pollution and child health. In: Schell LM, Ulijaszek SJ (eds). Urbanism, Health and Human Biology in Industrialised Countries. Cambridge: Cambridge University Press, 1999:136–157.
108. Schwartz J, Angle CR, Pitcher H. Relationship between childhood blood lead levels and stature. Pediatr. 1986;77:281–288.
109. Frisancho AR, Ryan AS. Decreased stature associated with moderate blood lead concentrations in Mexican-American children. AJCNA. 1991;54:516–519.
110. Ballew C, Khan LK, Kaufmann R, Mokdad A, Miller DT, Gunter EW. Blood lead concentration and children's anthropometric dimensions in the Third National Health and Nutrition Examination Survey (NHANES III) 1988–1994. J Pediatr. 1999;134:623–630.
111. Little BB, Snell LM, Johnston WL, Knoll KA, Buschang PH. Blood lead levels and growth status of children. Amer J Hum Biol. 1990;2:265–269.
112. Kafourou A, Touloumi G, Makropoulos V, Loutradi A, Papanagioutou A, Hatzakis A. Effects of lead on the somatic growth of children. Arch Envir Health. 1997;52:377–383.
113. Lauwers M-C, Hauspie RC, Susanne C, Verheyden J. Comparison of biometric data of children with high and low levels of lead in the blood. Am J Phys Anthropol. 1986;69:107–116.
114. Shukla R, Bonschein R, Dietrich KN, Mitchell T, Grote J, Berger OG, et al. Effects of fetal and early postnatal lead exposure on child's growth in stature—the Cincinnati Lead Study. In: Lindberg S, Hutchinson T (eds). Heavy Metals in the Environment. Edinburgh: CEP Consultants, 1987:210–212.

115. Shukla R, Bornschein R, Dietrich KN, Buncher C, Berger OG, Hammond P, et al. Fetal and infant lead exposure: effects on growth in stature. Pediatr. 1989;84:604–612.
116. Shukla R, Dietrich KN, Bornschein RL, Berger OG, Hammond P. Lead exposure and growth in the early preschool child: A follow-up report from the Cincinnati Lead Study. Pediatr. 1991;88:886–892.
117. Kim R, Hu H, Rotnitzky A, Bellinger D, Needleman HL. A longitudinal study of chronic lead exposure and physical growth in Boston children. Environ Health Perspect. 1995;103:952–957.
118. Danker-Hopfe H, Hulanicka B. Maturation of girls in lead polluted areas. In: Hauspie R, Lindgren G, Falkner F (eds). Essays on Auxology. Welwyn Garden City, UK: Castlemead Publications, 1995:334–342.
119. Huseman CA, Varma MM, Angle CR. Neuroendocrine effects of toxic and low blood lead levels in children. Pediatr. 1992;90:186–189.
120. Meyer MB, Tonascia J. Long-term effects of prenatal X-ray of human females. I. Reproductive experience. Amer J Epidemiol. 1981;114:304–316.
121. Brent RL. Effects of ionizing radiation on growth and development. In: Klingberg MA, Weatherall JAC, Papier C (eds). Epidemiologic Methods for Detection of Teratogens. New York: S. Karger Publishing, 1979:147–183.
122. Burrow GN, Hamilton HB, Hrubec Z. Study of adolescents exposed in utero to the atomic bomb, Nagasaki, Japan. JAMA. 1965;192:97–104.
123. Sutow WW, Conard RA, Griffith KM. Growth status of children exposed to fallout radiation on Marshall Islands. Pediatr. 1965;36:721–731.
124. Nakashima E, Carter RL, Neriishi K, Tanaka S, Funamoto S. Height reduction among prenatally exposed atomic-bomb survivors: A longitudinal study of growth. Health Physics. 1995; 68:766–772.
125. Hartikainen A-L, Sorri M, Anttonen H, Tuimala R, Laara E. Effect of occupational noise on the course and outcome of pregnancy. Scand J Environ Health. 1994;20:444–450.
126. Hartikainen-Sorri A-L, Kirkinen P, Sorri M, Anttonen H, Tuimala R. No effect of experimental noise on human pregnancy. Obstet Gynecol. 1991;77:611–615.
127. Wu T-N, Chen L-J, Lai J-S, Ko G-N, Shen C-Y, Chang P-Y. Prospective study of noise exposure during pregnancy on birth weight. Amer J Epidemiol. 1996;143:792–796.
128. Ando Y. Effects of daily noise on fetuses and cerebral hemisphere specialization in children. J Sound Vibration. 1988;127:411–417.
129. Rehm S, Jansen G. Aircraft noise and premature birth. J Sound Vibration. 1978;59:133–135.
130. Schell LM. The effects of chronic noise exposure on human prenatal growth. In: Borms J, Hauspie R, Sand A, Susanne C, Hebbelinck M (eds). Human Growth. New York: Plenum, 1982:125–129.
131. Schell LM. Environmental Noise and Human Prenatal Growth. Amer J Phys Anthropol. 1981;56:63–70.
132. Coblentz A, Martel A, Ignazi G. Effects of fetal exposition to aircraft noise on the birthweight of children. Proc Hum Factors Soc. 1990;562–566.
133. Ando Y, Hattori H. Statistical studies on the effects of intense noise during human fetal life. J Sound Vibration. 1973;27:101–110.
134. Knipschild P, Meijer H, Sallé H. Aircraft noise and birth weight. Inter Arch Occup Environ Health. 1981;48:131–136.
135. Takahashi I, Kyo S. Studies on the differences in adaptabilities to the noise environment in sexes and growing processes. J Anthropol Soc Nip. 1968;76:34–51.
136. Schell LM, Norelli RJ. Airport noise exposure and the postnatal growth of children. Am J Phys Anthropol. 1983;61:473–482.
137. Schell LM, Ando Y. Postnatal growth of children in relation to noise from Osaka international airport. J Sound Vib. 1991;151(3):371–382.

9

SOCIAL AND ECONOMIC INFLUENCES ON GROWTH AND SECULAR TRENDS

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INTRODUCTION

Relative to the myriad of species of the animal kingdom, humans are characterized by a heightened sensitivity to the environment, an attribute that permits individuals to respond to environmental changes while maintaining the homeostasis that characterizes them as mammals. Not only is this sensitivity seen as important physiologically, in a species such as *Homo sapiens*, with its large brain and complex neurological processes, it serves to enhance learning.

A further characteristic particular to human growth is the attenuation of the developing years and a concomitant slowing of the growth rate, leading to an increased time period for the interaction of the immature organism with his or her environment. This maximizes the opportunity for environmentally induced changes to become registered in the course both of physical growth and mental development (see, e.g., Ulijaszek, Johnston, and Preece[1]; Bogin[2]). Put another way, the length of the growth period as well as its plasticity makes the environments in which children grow and develop crucial.

When the environment supports the genetic template that regulates development, the resulting interaction is positive. Growth patterns respond to environmental pressures and the resulting attributes of the adult display adaptations to the ecosystem.[3,4] However, in today's world, many populations exist under conditions of great social and economic disadvantage, with poverty, malnutrition, disease, and overcrowding indicative of a spectrum of misery composing the environment within which millions of children grow to adulthood. Thus, the evolutionary adaptation for increased learning represented by an attenuated childhood has become, in more modern times, also a burden on the human population. Rather than providing a set of supportive experiences within which individuals may reach their genetic potential, the environment becomes for many not only a threat to life but also a systemic force that interferes with the achievement of their human potential as an adult member of society.

To consider the role of environmental forces in human growth is not to force a choice between "heredity and environment," which is indeed a false dichotomy. In his introduction to *Stature, Living Standards, and Economic Development* by John Komlos, James Tanner cites Thoday, a geneticist, as remarking that, "no characteristic is inherited; and none is acquired. All are developed."[5] This simple yet elegant statement lays out perhaps the fundamental precept of developmental biology; namely, that the expression of any trait emerges through the interaction of the genotype with the surrounding environment. The genotype carries the set of instructions necessary for the development of a mature, functioning adult, whatever the species. And variation in those instructions (i.e., genetic variation) can affect the ultimate size, structure, or behavior of the organism through differential effects on developmental pathways. But it is also true that the process of growth and development is carried out within a milieu of experiences and effects that interact with the genotype. It is this milieu that we call the environment.

Figure 9-1 shows the effects of the environment on growth in a sample of 2645 12-year-old boys of middle and low socioeconomic status (SES) from three schools in Guatemala City. The study from which the data are taken is described by Bogin and MacVean[6] and Johnston, Bogin, and MacVean.[7] The parents of middle SES were largely civil servants, teachers, and shopkeepers; while those of low SES were from an inner-city public (i.e., state) school in an area characterized by high rates of poverty. The graph gives the means of four commonly used measures of growth: height, weight, the sum of two skinfolds, and the estimated circumference of upper arm muscle. Skinfold thickness is a measure of fatness and arm muscle circumference of lean body mass.

The means of each variable are lower in the low SES sample than in the middle one. Given the design of the study, the most likely reason for the differences is to be found in the poorer environments of the children of low socioeconomic status. The mechanisms responsible have constrained—or depressed—the growth of these children.

ENVIRONMENT OF THE GROWING CHILD

The environment of a growing child may be conceptualized as anything external to the individual. It may be visualized as layered around the child, with the layers moving outward from the immediate and the idiosyncratic to those phenomena encompassing broad aggregate units, such as the natural world, the sociocultural

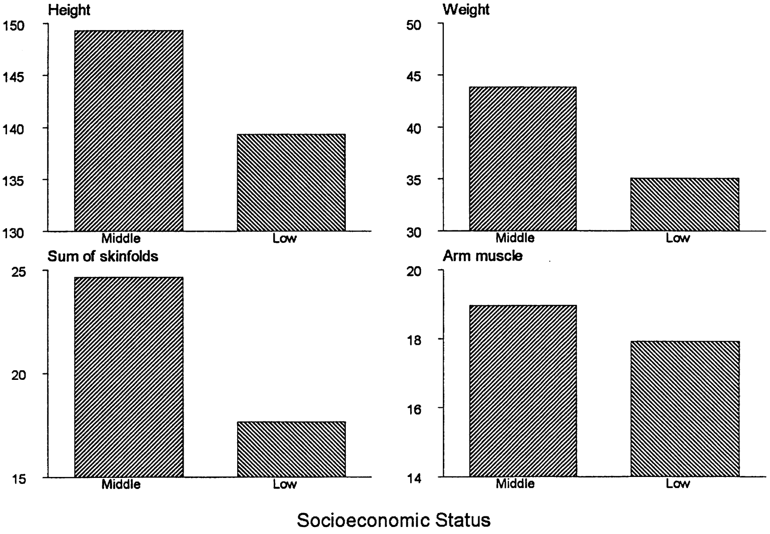

FIGURE 9-1 Mean height, weight, sum of skinfolds, and upper arm muscle circumference in Guatemala City 12-year-old boys of middle and low socioeconomic status.

context, the built environment, the ecosystem. Moving from the immediate to the global takes us along an axis of extending from the microscopic to the macroscopic.

Figure 9-2 presents a schematic diagram of the environment as represented by three axes along which effects may occur. These axes represent the environmental attributes of immediacy, intensity, and chronicity. The axis labeled *immediacy* represents the layering just discussed. A spectrum of potential environmental effects may be conceptualized along the axis moving from the microscopic to the macroscopic.

Figure 9-2 indicates two other axes useful for developing a concept of the effects of the environment. The second axis, labeled *intensity*, indicates effects that range from the mild through the moderate to the severe. The third axis indicates the *chronicity* of the effects, from short-term acute effects to those that are chronic and affect development throughout the growing years.

These axes are merely devices to aid us in understanding how the environment can affect development. As we combine them into a three-dimensional matrix, they begin to enclose a space that characterizes the environment in terms of potential effects. For example, an acute, short-term, and microscopic environment would be that of an inner-city child who, playing in the grass next to her house, inadvertently ingests flakes of a lead-based paint that, over the years, have fallen onto the ground. This one-time exposure of an individual child to a toxic dose of lead is likely to damage irreversibly her neurological development.

An example of a macroscopic, chronic environment is where the social and economic environment in which children grow up exerts constraints on development,

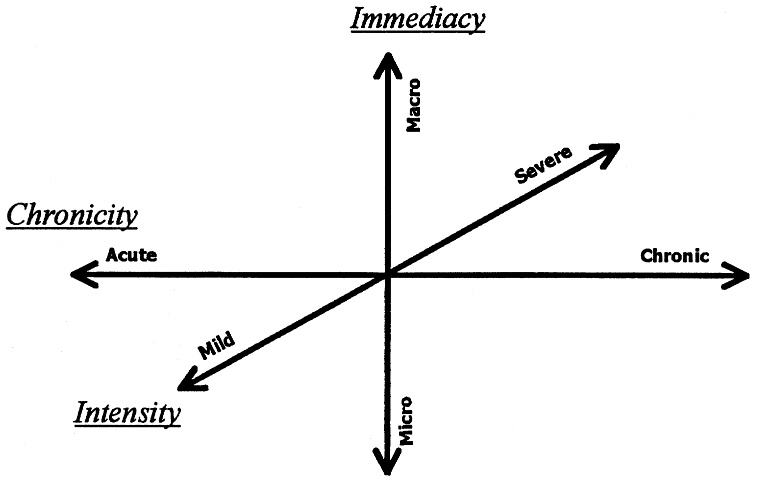

FIGURE 9-2 Schematic drawing of environmental effects on growth.

particularly in the case of those who are poor and socially marginal. Almost always, one finds poverty associated with low levels of education, substandard housing, large family size, high levels of infectious disease, increased mortality, and poor nutrition, usually at mild-to-moderate intensities. The greater the correlation of environmental components, the more pervasive is their effect on the individuals living under those conditions. Among those of lower social position, the association between components can be quite high, exerting a steady, downward constraining effect on the processes of development and, over time, producing often-marked effects. Bloom called such environments "powerful," in that not only are they extreme in their effects, but all-encompassing to the extent that virtually no one escapes the effects. The individual is altered by the environment while being relatively powerless to affect it.[8]

Of particular importance in understanding growth and development is the social environment of a child, those components traceable directly to the position of the child in its society. Obviously, social position is a cultural construct and depends heavily on the system of beliefs and symbols characteristic of a particular group and determined by traits of the child as well as traits associated with groups to which he or she belongs. Social position is therefore determined by a range of factors, such as, but not limited to, age, sex, status, economic position, physical location, ethnicity, and so on.

MODES OF ENVIRONMENTAL EFFECTS ON GROWTH

The environment may be thought of as presenting three modes of interaction with the developmental process. In the first mode, the course of growth and development is *unconstrained*, in that the impact of the environment does not interfere with the biological determinants of growth and provides a set of supportive experiences that permits the child to develop to genetic potential. This is what is meant when we speak of a "good" environment; that is, one in which development is not limited, or constrained, by surrounding conditions. In such a case, the major proportion of the variability among individuals reflects their genetic variability, individualized environmental experiences, and gene-environment interaction.

In the second mode of interaction, growth and development are channeled, or *patterned*, by forces external to the individual. As the child adapts to the pressures of the environmental milieu, growth is shaped in ways that lead to adults that are better adapted to the particular demands and stresses of the environment than someone who had grown up elsewhere. This aspect of human plasticity, termed a *developmental adaptation*,[9] has been utilized particularly effectively in interpreting why children who grow up at high altitude are better adapted than their parents that acclimatized to the stresses of such an ecosystem as adults. These observations have also been replicated in the laboratory with both rats and dogs.[9]

The third mode of interaction is one in which the environment *constrains* the developmental process. The results are distributed along a spectrum of outcomes, with any particular outcome depending on the intensity and chronicity of the constraint. In many instances, the impact is minor and, for example, in the case of growth, adult height, the outcome may be compromised by only a small amount. However, in many other instances, growth may not just falter but fail, indicative of systemic organic damage associated with impaired ability to expend energy, reduced cognitive functioning, and a shortened life expectancy.[1] In this sense, the physical measures of growth that are commonly taken by auxologists become indicators of an unfavorable growth history as well as a compromised physiological status.

The importance of the sensitivity of physical growth to adverse environmental conditions cannot be overemphasized. Tanner has written that " the growth of children amongst the various groups which make up a contemporary society reflects rather accurately the material and moral condition of that society.[10] Understanding the link between the growth status of the children of a community and the constraints imposed by the environment is the basis of "auxological epidemiology," the use of growth data as an indicator of the nutritional status and well-being of a community, a population, or a country.[11] The appropriate application of theory and method to the problem at hand provides information that can be used in evaluations of the current environment, in monitoring change in status over time, and in assessing responses in status resulting from programmatic interventions.[12]

In particular, the relationship between growth status and environmental quality is of use where the social and economic environment exerts its greatest constraints on development. Particularly in the case of the poor, as well as others who are socially and economically marginal, the components of the environment are highly correlated. Almost always, one finds poverty associated with low levels of education, substandard housing, large family sizes, high levels of infectious disease, increased mortality, and nutritional deficiency.

THE TIMING OF ENVIRONMENTAL EFFECTS

The environment begins to exert its effects on growth almost immediately after conception. Low dietary intakes of the nutrient folate can result in the failure of the neural tube of the embryo to close, a process that occurs usually before a woman is aware that she has conceived and can lead to serious neurological conditions such as spina bifida. And, even though the fetus is buffered against many harmful environmental forces, others can exert their effects. For example, mothers who experience a poor environment during their pregnancies have an increased risk of giving birth to an infant whose birth weight is low.

Chronic environmental effects that operate through the growing years can shape growth significantly. Figure 9-3 shows the curves of growth of height of Guatemala City schoolgirls from 6 to 17 years old of high and low socioeconomic status. The differences are established by the earliest age at which the individuals were measured and the curves are generally parallel until 12 years old, when they become greater due to effects on the timing of puberty. The difference narrows at 15 years old, as both samples reach the end of their pubertal spurt.

Differences in growth status associated with socioeconomic status are ubiquitous, being found in all regions of the world. Figure 9-4, after Martorell,[13] presents the mean heights of 7-year-old boys of high and low SES from various regions of the world. It is clear from the graph that the differences between the high and low SES samples within any region are greater than the differences within either SES group across regions. Furthermore, the bar to the right indicates the median height (50th percentile) of U.S. boys as compiled by the U.S. National Center for

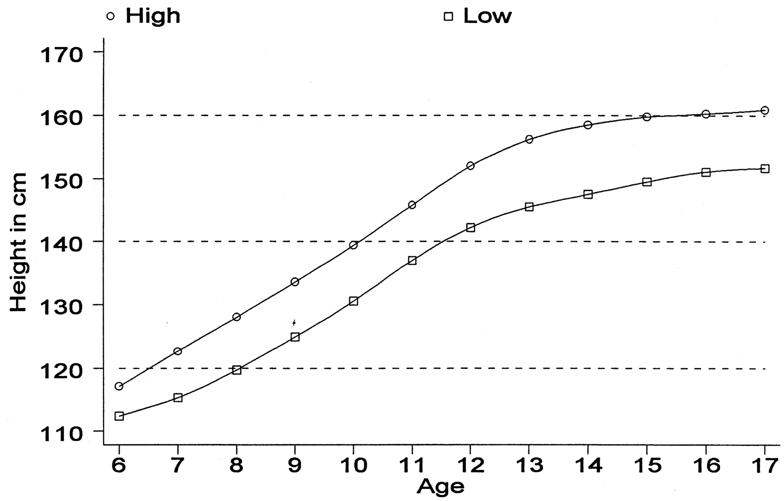

FIGURE 9-3 Growth in height of Guatemala City schoolgirls from 6 to 17 years old of high and low socioeconomic status.

Health Statistics (NCHS in the figure). The high SES means are very close to those of U.S. children. This suggests that, at least until age 7 and in the absence of significant environmental constraints, the average growth potential of children from around the world is similar to that characteristic of the developed economies.

The extent of deleterious environmental effects on the growth of children is seen in the prevalence of malnutrition, usually estimated from the percentage of preschool children whose growth status fell below a specific cutoff point, such as the 5th percentile of the reference standards. Figure 9-5, taken from the World Health Organization database,[14] shows the percentage of children from developing nations around the world classed as having low body weight (weight for age ≤ 2 *Z*-scores), stunted (height for age ≤ 2 *Z*-scores), or wasted (weight for height ≤ 2 *Z*-scores). In almost every instance, over 20% of the children are underweight and stunted. The low percentage assessed as wasted reflects the generally proportional effects of the environment on height and weight when the pressures are chronic and mild to moderate.

Differences associated with socioeconomic status, especially among the world's lesser-developed economies, are related to nutrition and disease factors that occur in early childhood. Such effects not only persist but are resistant to dietary intervention. In a study of the effects on development of nutritional supplementation to the diet of rural undernourished Guatemalan children, provision on food supplements before age 3 were associated with improvements in later growth and a reduction in mortality. On the other hand, if the supplementation occurred between 3 and 7 years old, there was no impact on growth, rate of maturation, or mental development.[15]

At the same time, more generalized improvements in the socioeconomic background during the growing years are associated with improved growth.[16] Figure 9-6 shows the amount of growth in stature over a 10-year period of children from a poor community located on the periphery of Guatemala City. The children are

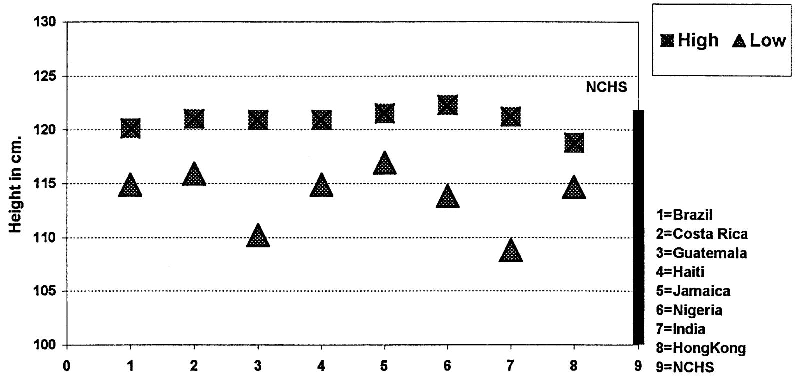

FIGURE 9-4 Mean heights of 7-year-old boys of high and low SES from various regions of the world. (Data from Martorell.[13])

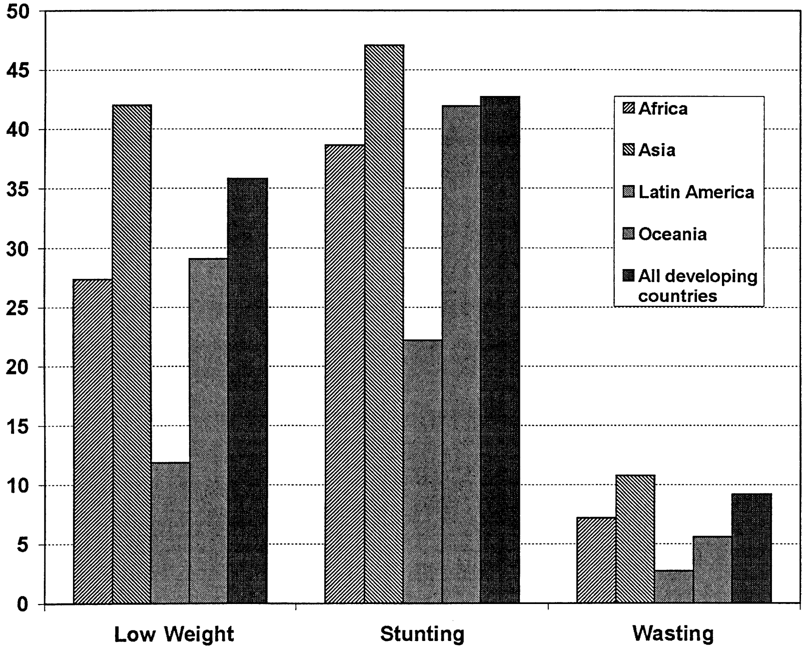

FIGURE 9-5 Estimated prevalence of malnutrition in developing countries. (WHO data from De Onis et al.[14])

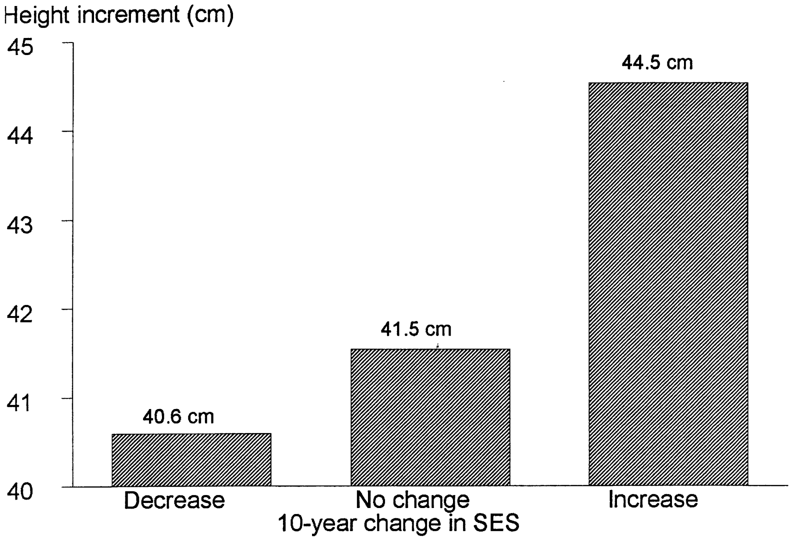

FIGURE 9-6 Ten-year increments of growth in stature of children from a poor Guatemalan community grouped by changes in the socioeconomic status of their families.

divided into three groups. The bar to the left represents children from families whose socioeconomic status declined over the 10-year period. The bar to the right represents those whose socioeconomic status improved and in the middle is of children whose families' SES did not change. These differences, which amount to 4 cm of growth between the two extreme groups, are statistically significant and demonstrate the dynamic relationship between the environment and growth, which can falter as the family environment worsens as well as improve when conditions become better.

SECULAR CHANGES, SECULAR TRENDS, AND GROWTH AND THE ENVIRONMENT

When applied to growth, the term *secular change* refers to changes over time in the characteristic pattern of growth of the children of a population.[17] Some authors use the word *trend* rather than *change*. However, others feel that *trend* implies a unidirectional movement over an extended time range and, since secular may be short or long term as well as positive or negative, have concluded that *secular change* is the better choice. In general—but not always—the phrase *secular trend* refers to longer-term, unidirectional changes, while *secular change* refers to any shift associated with time. Regardless of one's preference, changes that occur over time illustrate the dynamic nature of the interrelationship between growing children and their environment.

Figure 9-7, taken from Hauspie, Vercauteren, and Susanne,[18] demonstrates the long-term changes in the growth curves for the stature of Belgian children and youth measured on four occasions over a period of 150 years. Between 1830 and 1980–1982, the average secular trend was 0.7 cm/decade in children and 0.8 cm/decade in youth in both sexes. Given that the changes during the adolescent years were almost the same as during childhood, the authors concluded that, "the secular increase in height . . . was due solely to an upward shift of stature at all ages and not to a secular change in tempo of growth" (p. 9).

Similar trends over long periods of time have been described by numerous authors and may be found in various publications (e.g., Van Wieringen[17]; Eveleth and Tanner[19]; Roche[20]; Tanner[21]).

Even though some authors have attributed a variety of causes to the secular trend, there seems to be near universal agreement at present that the secular changes studied by auxologists and other scientists reflect changes in environmental conditions. Bielicki[22] wrote that, "the evidence is compelling that secular trends . . . are purely phenotypic responses to changes in living standards" (p. 303).

METHODOLOGICAL ISSUES

While methodological rigor is crucial in any research, it seems especially so in studies of secular trends, since so many confounding factors can lead to erroneous

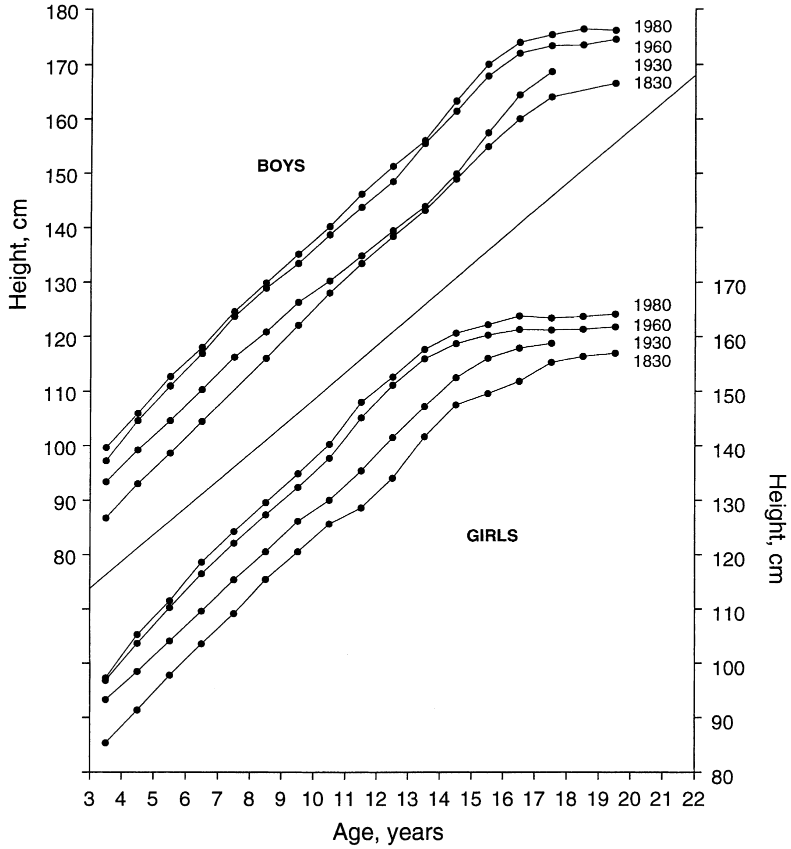

FIGURE 9-7 Secular increase in stature in Belgian children and youth over 150 years. (Source: Hauspie, Vercauteren, and Susanne.[18] Reproduced with kind permission of the author and publishers.)

conclusions. The majority of studies have dealt with the mean heights of samples of adults, due most likely to the relative ease of obtaining data, and the need not to be concerned with growth per se. Since adult height is the result of the course of growth, many authors then conclude that they have detected differences in growth patterns. However, this is not always the case. From approximately 30 years of age, a loss of stature is associated with increasing age in humans, due to a variety of factors, such as bone loss, a reduction in the elasticity of intervertebral cartilage, and the like; unless there is a correction for age, erroneous conclusions may result.

The study of secular change in children may also be subject to error. Interpreting differences in, for example, physical growth between two birth cohorts of children may be confounded by secular effects on the rate of maturation. Figure 9-8 presents the average height of 52,699 Guatemala City boys of high SES. The sample is divided into groups: The one labeled *delayed* consists of those who were the slowest-maturing 30%, as indicated by their skeletal age. The one labeled *advanced* is the fastest-maturing 30%. The bars represent the mean height at each age. Clearly, the children and youth of the advanced group are taller than those of the delayed, the differences becoming greater during the adolescent years, when advanced boys commence their growth spurt at an earlier age than the delayed one. In comparing the growth curves of children measured in different decades—even centuries—one must have some idea of to what extent the differences reflect changes in growth, if the focus is upon growth and not maturation.

Nonetheless, studies of secular growth changes demonstrate many consistent trends. Roche[20] noted the following:

- Rates of growth have increased considerably during the past 50–100 years.
- There is an increase in the rate of maturation seen especially in the age at menarche.
- These changes have occurred in all developed countries but are less consistent in lesser developed economies.
- Changes in body proportions are less marked than are those in body size.
- Changes in body fatness have largely been among the upper percentiles of adiposity.

While agreeing in general with these conclusions, Malina[23] noted the existence of negative trends in some populations, most notable a decline in stature in Europe

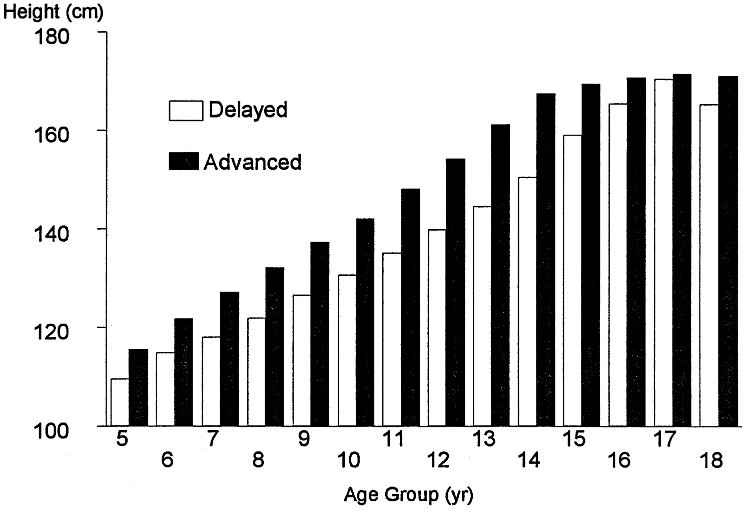

FIGURE 9-8 Mean heights of 52,699 Guatemala City boys of high SES according to their rates of maturation.

from about the eleventh to the nineteenth centuries. A lack of consistency is not unexpected. If secular changes reflect environmental factors, then they reflect, on the one hand, widespread improvements in nutrition and health status, while, on the other, more localized improvements and declines. Nonetheless, the changes can be considerable. Floud[24] reported an almost 15 cm increase in the mean height of conscripts in the Netherlands, Denmark, Sweden, and Norway between 1860 and 1980.

Not all secular changes are desirable, as far as health status is concerned. In many parts of the world, measures of growth such as height show no change while indicators of body fatness are increasing. Greater levels of adiposity without a corresponding change in height is associated with an increased prevalence of overweight and obesity, known to be a health risk among children and adolescents.[25,26] Such changes have been reported, for example, in Germany[27] and the United States.[28]

Increasing levels of childhood fatness have also been observed in lesser-developed nations. Figure 9-9 shows secular change in height and adiposity, measured here as the sum of the triceps and subscapular skinfolds, in 12-year-old Guatemala City boys of middle and low SES over a period of 20 years.[29] To facilitate comparison, the raw measurements have been converted to standardized Z-scores, which have a mean of 0 and a standard deviation of 1.0. The figure shows the mean Z-scores for each of four 5-year periods and indicates clearly that middle SES boys

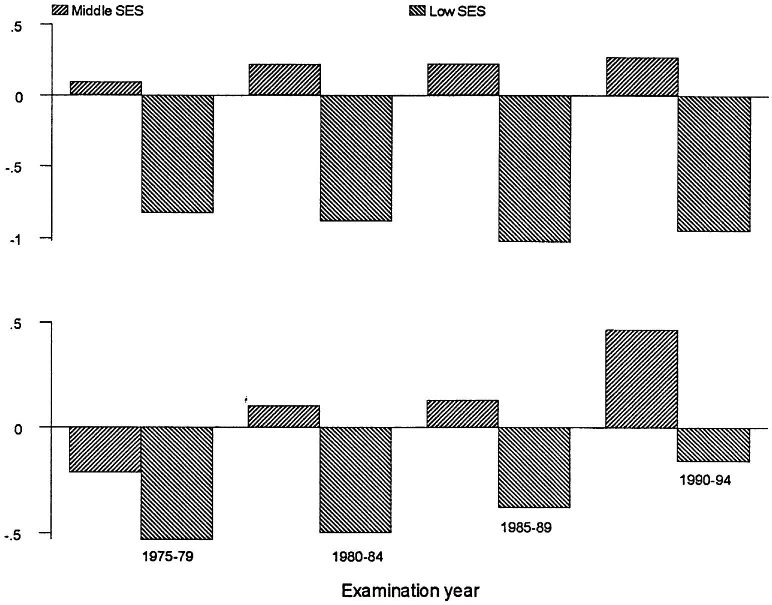

FIGURE 9-9 Mean height and sum of skinfolds of 12-year-old Guatemala City boys of middle and low SES by year of measurement.

are taller and fatter than are those from poor homes. Furthermore, it reveals no significant change in height in either group. However, there are steady and significant changes in fatness levels in both groups, to the extent that the low SES boys measured in 1990–1994 are as fat as their middle SES age peers measured in 1975–1979.

While the secular trends observed in many parts of the world over long periods of time are generally considered to indicate relaxation of constraints on growth associated with improved environmental conditions, the greater sensitivity of body fatness to the environment is becoming an increased concern for public health workers. The problem becomes even more severe in those regions characterized by chronic undernutrition and high incidence of infectious disease, because growth during the early years is likely to falter with stunting as a predictable outcome. However, the responsiveness of adipose tissue to the nutritional ecosystem of the child, along with the reduced demand for dietary energy as growth begins to slow, is increasingly being seen to result in higher levels of overweight—even obesity—in such settings.[30]

CONCLUSION

Humans are characterized by a longer period of growth and a greater sensitivity to environmental stimuli than other animals. These attributes have become elaborated during the course of evolution and serve to enhance learning and adaptation to ecological pressures. This sensitivity and its implications are easily demonstrated and have been a major focus of research in child development throughout the last century and continues to the present day. Such a statement in no way reduces the role of the genotype in growth but emphasizes the dynamic relationship and close interaction between genes and the ecosystem in which they are expressed.

At the same time, the environments in which humans live and that they construct and create can have deleterious effects on an organism that displays significant ecosensitivity. The result of the organism-environment interaction is seen in the range of variability in growth patterns among individuals, but particularly among populations—contemporary, historical, and prehistoric. The growth status of children then is not only shaped by their environment but also provides a reliable indicator of the degree of constraint exerted by it on growth.

REFERENCES

1. Ulijaszek SJ, Johnston FE, Preece MA (eds). The Cambridge Encyclopedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998.
2. Bogin B. Patterns of Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1999.
3. Little MA. The development of ideas about human ecology and adaptation. In: Spencer F (ed). A History of American Physical Anthropology, 1930–1980. New York: Academic Press, 1982: 405–434.

4. Frisancho AR, Greksa LP. Developmental responses in the acquisition of functional adaptation to high altitude. In: Little MA, Haas JD (eds). Human Population Biology, a Transdisciplinary Science. Oxford: Oxford University Press, 1989:203–221.
5. Tanner JM. Introduction: Growth in height as a mirror of the standards of living. In: Komlos J (ed). Stature, Living Standards, and Economic Development. Chicago: University of Chicago Press, 1994:1–6.
6. Bogin B, MacVean RB. Growth in height of urban Guatemalan primary school children of high and low socioeconomic class. Hum Biol. 1978;50:477–488.
7. Johnston FE, Bogin B, MacVean RB. A comparison of international standards versus local reference data for the triceps and subscapular skinfolds of Guatemalan children and youth. Hum Biol. 1984;56:157–171.
8. Bloom BS. Stability and Change in Human Characteristics. New York: Wiley, 1964.
9. Komlos J (ed). Stature, Living Standards, and Economic Development. Chicago: University of Chicago Press, 1994.
10. Tanner JM. Growth as a mirror of the condition of society; secular trends and class distinctions. In: Demirjian A (ed). Human Growth, A Multidisciplinary Review. London: Taylor and Francis, 1986:3–34.
11. Tanner JM. A History of the Study of Human Growth. Cambridge: Cambridge University Press, 1990.
12. Himes JH (ed). Anthropometric Assessment of Nutritional Status. New York: Wiley, 1991.
13. Martorell R. Child growth retardation: A discussion of its causes and its relationship to health. In: Blaxter K, Waterlow JC (eds). Nutritional Adaptation in Man. London: Libbey, 1985:13–30.
14. De Onis M, Monteiro C, Akré J, Clugston G. The worldwide magnitude of protein-energy malnutrition: An overview from the WHO Global Database on Child Growth. Bull WHO. 1993;71:703–712.
15. Martorell R, Scrimshaw NS (eds). The effects of improved nutrition in early childhood: The Institute of Nutrition of Central America and Panama (INCAP) follow-up study. J Nutrit. 1995;125(Suppl):1027S–1138S.
16. Johnston FE, MacVean RB. Growth faltering and catch-up growth in relation to environmental change in children of a disadvantaged community from Guatemala City. Amer J Hum Biol. 1995;7:731–740.
17. Van Wieringen JC. Secular growth changes. In: Falkner F, Tanner JM (eds). Human Growth, 2nd ed., Vol. 3. New York: Plenum, 1986:307–331.
18. Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth. Horm Res. 1996;45(Suppl 2):8–17.
19. Eveleth PB, Tanner JM. Worldwide Variation in Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1990.
20. Roche AF (ed). Secular trends in human growth, maturation, and development. Monogr Soc Res Child Dev. 1979;44(Serial 179):3–4.
21. Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1969.
22. Bielicki T. Secular trends in growth: Human biologists' contribution to the understanding of social change. In: Johnston FE, Zemel B, Eveleth PB (eds). Human Growth in Context. London: Smith-Gordon, 1999:303–311.
23. Malina RM. Research on secular trends in auxology. Anthrop Anz. 1990;48:209–227.
24. Floud R. The heights of Europeans since 1750: A new source for European economic history. In: Komlos J (ed). Stature, Living Standards, and Economic Development. Chicago: University of Chicago Press, 1994:9–24.
25. Johnston FE. Health implications of childhood obesity. Ann Int Med. 1985;103:1068–1072.
26. Rolland-Cachera MF. Obesity among adolescents: Evidence for the importance of early nutrition. In: Johnston FE, Zemel B, Eveleth PB (eds). Human Growth in Context. London: Smith-Gordon, 1999:245–258.
27. Kromeyer-Hauschild K, Jaeger U. Growth studies in Jena, Germany: Changes in body size and subcutaneous fat distribution between 1975 and 1995. Amer J Hum Biol. 1998;10:579–587.

28. Gordon-Larsen P, Zemel BS, Johnston FE. Secular change in stature, weight, fatness, overweight, and obesity in urban African-American adolescents from the mid-1950s to the mid-1990s). Amer J Hum Biol. 1997;9:675–688.
29. Johnston FE, Baessa Y, MacVean RB. Secular changes in skinfold thickness over 20 years of Guatemala City 12 year olds of high, middle, and low socioeconomic status. Revista Española de Antropología Biológica. 1999;20:75–83.
30. Peña M, Bacallao J (eds). Obesity and Poverty: A New Public Health Challenge. Washington, DC: Pan American Health Organization, 2000.

10

ENDOCRINE DISORDERS OF GROWTH

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INTRODUCTION

Normal growth involves differentiation of cells, formation of organs and tissues, expansion of cell numbers, and increases in the size of individual cells en route to the production of a mature organism. Generation, transmission, and recognition of signals between cells constitutes an essential aspect of growth. These signals may act at a short range (e.g., paracrine signaling) or at a long range (e.g., endocrine signaling). This chapter focuses on hormonal signals produced by one cell type, released into the circulation, and influencing the growth or the function of cells in target tissues.

Study of individuals whose growth departs from normal has produced important insights into the contributions of hormonal signaling to normal growth. The evaluation of a person who is unusually small or large for his or her age begins with the characterization of the growth phenotype. It continues with the measurement of the hormones known to influence growth or the hormonal phenotype. The third level involves finding an explanation for hormone deficiency or excess. Is the problem caused by an acquired disease process or is it caused by a genetic abnormality? Over the past two decades, advances in molecular genetics have permitted recognition of specific genetic defects that explain many disorders of growth. Studies of naturally occurring mutations reflecting experiments of nature have been complemented by gene knockout experiments in animals.

We outline the steps involved in characterization of abnormal growth, apply them to an individual with profoundly abnormal growth, and consider alternative explanations for the growth disturbance.

CHARACTERIZATION OF ABNORMAL GROWTH

Growth Phenotype

Five questions need to be addressed in defining a growth phenotype:

1. How does recumbent length before 2 years of age or standing height after 2 years of age compare to the mean for persons of the same age and gender? Stature is plotted on an appropriate growth chart and expressed as a percentile value or the number of standard deviations above or below the mean (see Chapters 16 and 18).
2. How does the individual's stature compare to their parents' statures? The height of the like-sex parent is entered on the growth chart. There is, on average, a 12.5 cm or 5 in. difference between male and female height. Males experience 2 more years of childhood growth than females and have a slightly more intense pubertal growth spurt. Therefore, one adds 12.5 cm to the mother's height to plot it on a male chart and subtracts 12.5 cm from the father's height to plot a sex-adjusted male height on a female growth chart.
3. How did the individual arrive at his or her current height? Past height measurements are entered on the chart to determine when growth departed from normal. Did the departure begin before birth, during infancy, during childhood, or at the age when children normally begin a pubertal acceleration of growth?
4. How does weight compare to stature? Weight is plotted on a weight-for-age chart. Having done this, one can gain more insight into the relationship between weight and height by using a weight-for-stature chart or by calculating the body mass index (BMI) (weight in kg/height in m^2) and plotting it on a chart of BMI percentiles as a function of age and gender.
5. How does pubertal development compare to other persons of the same age and gender? Pubertal development is scored by the Tanner system for breast and pubic hair development in females and for genital and pubic hair development in males (see Chapter 17).

Hormonal Phenotype

Measurement of circulating levels of the relevant hormones is crucial in defining the intermediate phenotype. This term denotes the characteristics that lie between the cause of the disorder and its observed effects on growth. Different sets of hormones influence growth at different stages, so one needs to be selective in choosing which hormones to assess. Some can be assessed by a single blood test in the basal state (e.g., prolactin) and others require dynamic testing, in which one administers a challenge and measures a response (e.g., growth hormone). It is useful to consider a single hormone as a member of an axis or a coordinated, multilevel pathway for the flow of information. Evaluation of different steps along the pathway can often pinpoint the locus of a defect. Each needs to recognize a signal, act on it, and pass along another signal. It is seldom possible to measure the signal from hypothalamus to pituitary directly. These signals are short-lived, travel in a local vascular system, and are diluted and degraded on entry into the systemic circulation. It is eminently possible to measure pituitary hormones and the peptide, iodothyronine, or steroid hormones that they influence. Measurement of the hormonal signals belonging to several different pathways can disclose whether the disease process affects only one pathway or several different axes (Table 10-1).

Growth Hormone Axis

Pituitary growth hormone (GH) is a 191 amino acid protein hormone produced by somatotrope cells in the anterior pituitary. This hormone is also known as somatotropin. It is closely related to chorionic somatomammotropin (also known as *placental lactogen*) and a placental growth hormone produced by syncytiotrophoblastic cells of the fetal placenta. The GH-1 gene encoding pituitary growth hormone precedes the CS-P pseudogene and the CS-1, GH-2, and CS-2 genes that lie in a five-gene cluster on the short arm of human chromosome 17 (Figure 10-1). Studies of growth in persons who lack the GH-1 gene show that pituitary GH makes a small contribution to fetal growth during the third trimester and is essential for normal postnatal growth.

Growth hormone secretion is pulsatile rather than continuous. Peaks of circulating growth hormone occur during sleep and following intense exercise. Neural signals provoke secretion of a 40 and 44 amino acid growth-hormone-releasing hormone (GHRH) species from cells in the supraoptic nucleus of the hypothalamus. This neuroendocrine signal is secreted into the capillary plexus of the median eminence and reaches the anterior pituitary through the hypothalamic-pituitary portal circulation that traverses the pituitary stalk or infundibulum connecting the brain and anterior pituitary. GHRH binds to a GHRH receptor on the surface of somatotropes. This receptor is a member of the "seven-membrane spanning domain" family of hormone receptors.[1] Occupancy of the receptor activates a G-protein, which in turn activates adenylyl cyclase. An increase in intracellular cyclic AMP results in the release of GH from secretory granules into the systemic circulation. The action of GHRH on GH release is balanced by that of a 15 amino acid growth somatotropin-release inhibiting factor (SRIF) called *somatostatin*. This hormone also inhibits release of thyroid-stimulating hormone (TSH). Both GHRH and somatostatin are required for sustained synthesis of GH between secretory episodes.

Growth hormone binds to specific receptors on the surface of target cells in the liver, cartilage, and other tissues. The GH-receptor (GH-R) is a 620 amino acid protein with an extracellular ligand-binding domain, a transmembrane domain, and

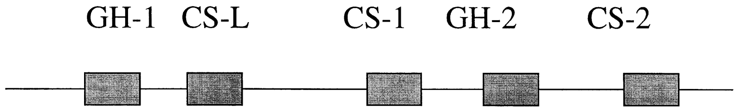
TABLE 10-1 The Hypothalamic-Pituitary-Gland-Target Tissue Axes

			Phenotypic Consequences of Deficiency			
Growth Hormone Component	Function	Organ/Tissue of Origin	Growth	GH	IGF-1	IGFBP-3
Somatostatin	Inhibits GH release	Hypothalmus	↑	↑	↑	↑
GH releasing hormone	Stimulates GH release	Hypothalmus	↓	↓	↓	↓
GHRH receptor	Transmits GHRH signal	Anterior pituitary	↓	↓	↓	↓
Growth hormone	Indirectly stimulates growth	Anterior pituitary	↓	↓	↓	↓
GH receptor	Transmits GH signal	Liver, others	↓	↑	↓	↓
Insulin-like growth factor 1	Directly stimulates growth Inhibits GH release	Liver, others Anterior pituitary	↓	↑	↓	↑
IGF-1 receptor	Transmits IGF-1 signal	Cartilage, others	↓	↑	↑	↑

			Phenotypic Consequences of Deficiency		
Thyroid Component	Function	Organ/Tissue of Origin	Growth	T_4	TSH
TRH	Stimulates TSH release	Hypothalamus	↓	↓	↓
TSH	Stimulates T_4, T_3 production	Pituitary	↓	↓	↓
T_4, T_3	Circulating thyroid hormones	Thyroid	↓	↓	↓
Thyroid hormone receptor	Transmits T_4, T_3 signals	Many	↓	↑	↑

			Phenotypic Consequences of Deficiency		
Gonadotropin Component	Function	Organ/Tissue of Origin	Growth	Testo/E_2	LH, FSH
LHRH	Stimulates LH, FSH	Hypothalamus	↓ (Complex)	↓	↓
LH, FSH	Stimulates sex hormones	Pituitary	↓ (Complex)	↓	↓
Testosterone, estradiol	Circulating sex hormones	Testes, ovaries	↓ (Complex)	↓	↑
Sex hormone receptors	Transmit sex hormone signals	Many	↓ (Complex)	↑	↑

			Phenotypic Consequences of Excess		
Glucocorticoid Component	Function	Organ/Tissue of Origin	Growth	Cortisol	ACTH
Corticotropin releasing factor	Stimulates ACTH	Hypothalamus	↓	↑	↑
ACTH	Stimulates cortisol production	Pituitary	↓	↑	↑
Cortisol	Circulating steroid	Adrenal cortex	↓	↑	↓
Glucocorticoid receptor	Transmits cortisol signal	Many	↓	↓	↓



Gene	Product	Concentration	
GH-1	Pituitary GH	4 μg/L	
CS-L	None	NA	
CS-1	CS aka PL	2 mg/L	(maternal)
GH-2	Placental GH	40 μg/L	(maternal)
CS-2	CS aka PL	2 mg/L	(maternal)

FIGURE 10-1 The positioning of the GH-1 gene on the short arm of human chromosome 17.

a cytoplasmic signaling domain. Binding of GH to one receptor molecule is followed by binding of a second growth hormone receptor (GH-R) molecule. This dimerization of two GH-R molecules around one GH molecule activates a receptor-associated Janus kinase, which sets in motion a cascade of events leading to an increase in expression of the insulinlike growth factor 1 (IGF-1) and its major circulating binding protein, IGF-binding protein 3 (IGF-BP3). When IGF-1 is released from the target cell it, in turn, binds to cell surface receptors and influences the activity of cartilage-forming cells at the growth plate. The GH and IGF-1 axis has both endocrine and paracrine aspects. Production of IGF-1 by liver cells is responsible for the majority of circulating IGF-1, and circulating IGF-1 can stimulate growth. This is an endocrine mechanism for promotion of growth. In this context, the liver functions as an endocrine organ, producing a hormone that influences the activity of target tissues. IGF-1 is also produced at the growth plate and can act locally through a paracrine mechanism. Transgenic mouse models involving selective inactivation of the IGF-1 gene in liver cells show very low levels of circulating IGF-1 but relatively normal growth because the paracrine IGF-1 system is preserved.[2]

Disorders

Clinical evaluation of the growth hormone axis begins with measurement of the levels of circulating IGF-1 and IGF-BP3. The observed levels are compared with the normal ranges for age and sex, keeping in mind that levels are low during infancy, increase during childhood, and peak during adolescence (see Chapter 7). Finding low IGF-1 and IGF-BP3 levels prompts measurement of GH. The combination of low IGF-1 and IGF-BP3 levels and a high resting GH level suggests insensitivity to the action of growth hormone. This genetic disorder was originally described by Laron, Pertzelan, and Mannheimer in 1966.[3] Laron syndrome is now known to be caused by mutations of the GH-R gene.[4]

Further insight can be gained by measuring levels of growth-hormone-binding protein (GHBP). This protein is released into the circulation by enzymatic cleavage of GH-R at the junction of the extracellular and transmembrane domains. Levels of GHBP are determined by the nature of the mutation. They may be undetectable with mutations leading to loss of binding activity, normal with mutations that preclude dimerization, and high with mutations that lead to loss of the intracellular domain.[5] The combination of high GH, low IGF-1 and normal IGF-BP3 suggests a problem distal to the GH receptor. There has been only one report of an abnormality in the IGF-1 gene.[6] This child was homozygous for a partial deletion of the gene. He experienced prenatal as well as postnatal growth retardation and also demonstrated mental retardation and deafness.

Most persons with growth retardation and abnormalities of the growth hormone axis have low IGF-1, low IGF-BP3, and a low resting GH level. Because GH levels are low in most people most of the time, further testing is required to see whether there is a defect in GH secretion. It is possible to measure GH release during sleep or following strenuous exercise but most testing involves use of a pharmacological stimulus. The procedure involves obtaining a baseline sample, giving an agent known to provoke GH release, and taking several poststimulus samples to assess response. Commonly used stimuli include clonidine, L-DOPA, arginine, and insulin. Clonidine is an alpha adrenergic agonist and L-DOPA is a dopaminergic agonist that evoke GH release through release of GHRH. Arginine is an amino acid that inhibits somatostatin release. Insulin causes a fall in blood glucose that in turn causes GHRH release. The failure to achieve at least one GH value above the somewhat arbitrary value of 10 ng/ml during two tests supports a diagnosis of growth hormone deficiency. Defects may reside at the level of neural modulation of GHRH and somatostatin secretion, at the level of the hypothalamus, or at the level of the anterior pituitary. Pituitary defects are further characterized by failure to release GH following direct stimulation with synthetic GHRH, with or without inhibition of somatostatin release by prior administration of arginine or physostigmine. Virtually all the recognized genetic forms of GH deficiency affect the pituitary level and consist of mutations in genes encoding transcription factors required for somatotrope function, in the gene for the GHRH receptor, or in the GH-1 gene.

Thyroid Hormone Axis

Like the growth hormone axis, the thyroid hormone axis includes central nervous system, hypothalamic, pituitary, target organ, and target tissue components. Neural inputs influence hypothalamic function. Cells in the paraventricular nucleus of the hypothalamus produce the tripeptide gly-his-pro thyrotropin-releasing hormone (TRH). This is produced through enzymatic cleavage of a 242 amino acid preprohormone containing six copies of the TRH sequence. The releasing hormone reaches the anterior pituitary through the hypothalamic pituitary portal circulation. TRH binds to a specific receptor on thyrotropes and promotes release of thyrotropin, also known as *thyroid-stimulating hormone* (TSH). The positive effect of TRH on TSH is opposed by the release-inhibiting action of somatostatin. Secretion of TSH is reasonably stable over time, with a small nocturnal surge. Negative feedback control is exercised at the pituitary and hypothalamic levels by thyroid hormones.

The pituitary hormone TSH binds to specific receptors on the surface of thyroid follicular cells and activates a G-protein coupled pathway to increase intracellular cyclic AMP. Receptor occupancy increases production of thyroglobulin as well as pinocytosis of thyroglobulin, coupling of iodothyronine molecules, and release of thyroid hormones into the systemic circulation.

Active thyroid hormones consist of tetraiodothyronine (T4) and triiodothyronine (T3). The more abundant T4 is released by the thyroid gland and the less abundant but more potent T3 is both produced by the thyroid and generated peripherally through outer ring deiodination of T4. More than 99% of circulating thyroid hormone molecules are bound to a high-affinity thyroxine-binding globulin. Cells see only the free or unbound hormone. Thyroid hormones influence gene transcription via a nuclear thyroid hormone receptor. The thyroid hormone receptor has a ligand-binding domain and a DNA-binding domain. The occupied hormone receptor complex binds to promoter sites in target genes and either promotes or inhibits transcription of these genes.

Disorders

The thyroid gland has migrated from the base of the tongue to its definitive location below the thyroid cartilage and thyroid hormone production is well underway by 12 weeks after conception. Before this time, the fetus is dependent on transplacental passage of thyroid hormones from the maternal circulation and untreated maternal hypothyroidism can have lasting effects on hearing and intelligence. Failure of thyroid development has little effect on fetal growth in length or weight, but skeletal maturation is delayed. In the rare circumstance of fetal hypothyroidism and untreated maternal hypothyroidism, there is normal linear growth but impaired maturation of the lungs and cardiovascular system as well as the skeleton.[7] Congenital or acquired hypothyroidism profoundly impairs postnatal growth and skeletal maturation. The age of onset of acquired hypothyroidism can often be established through detection of a point of inflection in the growth curve or examination of a hand and wrist X ray for bone age.

Clinical assessment of the thyroid axis starts with a measurement of T4, T3, and TSH. One can order a direct measurement of free T4 or request measurement of total T4 together with an assessment of the degree of saturation of thyroxine-binding globulin (total T4 × T3 uptake = free thyroxine index). A low free T4 together with a high TSH points to primary hypothyroidism. In this context, *primary* denotes that the defect is at the level of the thyroid gland. A low free T4 together with an inappropriately low TSH points to either secondary hypothyroidism, with the defect residing at the level of the thyroid gland, or tertiary hypothyroidism, with the defect residing at the level of the hypothalamus. Levels of T3 tend to be closer to the normal range in these conditions, due to increased peripheral conversion of T4 to T3. Levels of T3 tend to be lower than those of T4 in conditions of starvation and nonthyroidal illness in which there is both hypothalamic and peripheral downregulation of thyroid activity. A TRH stimulation test is used to distinguish between secondary and tertiary hypothyroidism. When there is pituitary destruction or a genetic defect involving transcription factors necessary for somatotrope development or function, little or no increase in TSH levels is found following intravenous injection of TRH. Levels of TSH rise following TRH stimulation in persons with hypothalamic or tertiary hypothyroidism, but the rise may be less prompt and more prolonged than in normal individuals.

Another type of hypothyroidism involves end organ insensitivity and is thus analogous to the Laron syndrome of growth hormone insensitivity. It is characterized by high TSH together with high free T4 and T3 levels and reflects abnormalities of the thyroid hormone receptor gene. Most cases have involved heterozygosity for mutations within the hormone binding domain.[8]

Gonadotropin Axis

The gonadotropin axis directs sexual differentiation during fetal life, acceleration of growth during puberty, development of secondary sexual characteristics, and the achievement of reproductive capacity. Hypothalmic neurons produce a 10 amino acid gonadotropin-releasing hormone (GnRH) through cleavage of a 92 amino acid precursor. Secretion is pulsatile, with intervals of about 60 minutes between peaks. The GnRH binds to a specific membrane receptor on the surface of gonadotropes in the anterior pituitary gland. Pulsatile exposure to GnRH leads to synthesis and secretion of the two gonadotropic hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). They, in turn, bind to separate LH and FSH receptors on the surface of testicular and ovarian cells. LH alone is sufficient to stimulate growth of Leydig cells and production of testosterone. Both FSH and a high local concentration of testosterone are essential for proliferation of seminiferous tubules and sperm production. Both LH and FSH are necessary for ovarian growth and production of estradiol.

Disorders

Laboratory evaluation of the gonadotropin axis begins with measurement of LH, FSH, and testosterone in males and of LH, FSH, and estradiol in females. The observed values are compared to normal ranges for age and gender. Gonadotropin and sex hormone levels are normally very low in childhood. It is generally not possible to use static measurements of these hormones to determine whether puberty will be delayed or there will be a lifelong deficiency in LH and FSH. Intravenous administration of synthetic GnRH is sometimes more helpful. It is common for prepubertal children to show a rise in FSH following GnRH, and the absence of an FSH response may predict permanent central hypogonadism. When the problem involves a gonadal defect, as in Turner syndrome, the basal levels of LH and particularly FSH tend to lie above the normal adult range.

Glucocorticoid Axis

Neurons in the paraventricular and supraoptic nuclei of the hypothalamus produce and secrete corticotropin-releasing hormone. This 41 amino acid peptide is produced by enzymatic cleavage of a 191 amino acid preprohormone (CRH). It binds to a CRH receptor on the surface of corticotropes and stimulates production of corticotropin (ACTH). The 39 amino acid ACTH is produced by enzymatic cleavage of proopiomelanocortin (POMC). Cleavage of POMC also produces alpha lipotropin, beta-lipotropin, alpha-MSH, beta-MSH, beta-endorphin, and a corticotropin-like intermediate lobe peptide (CLIP). Transcription of the POMC gene is inhibited by cortisol. Corticotropin enters the systemic circulation, binds to an ACTH receptor on the surface of steroid-producing cells in the adrenal cortex. Tonic exposure to ACTH sustains adrenal cortical cells and exposure to pulses of ACTH stimulates production and release of cortisol. This hormone, in turn, binds to a glucocorticoid receptor and influences transcription of a large variety of genes.

Disorders

Cortisol deficiency can produce failure to thrive with poor linear growth and failure to gain weight. It can also lead to hypoglycemia and sudden death. Glucocorticoid excess impairs linear growth but augments adipose tissue growth and weight gain.

Laboratory evaluation of the glucocorticoid axis begins with measurement of cortisol and ACTH. Levels tend to be higher in the morning hours and lower in the afternoon and evening, reflecting normal diurnal variation. The combination of a low morning cortisol and a low ACTH suggests a defect at the level of the hypothalamus or pituitary. A low cortisol together with a high ACTH value points to a defect at the level of the adrenal glands. Additional information can be provided by dynamic tests. Failure to raise cortisol in response to acute stimulation with synthetic CRF or synthetic ACTH is compatible with either a central or an adrenal defect. Persons with central defects eventually show a rise in serum cortisol with repeated doses of ACTH, whereas those with an adrenal defect do not.

Excessive production of cortisol is reflected in chronically high cortisol levels and loss of diurnal variation in serum cortisol. Persons with Cushing syndrome due to a corticotrope adenoma show exaggerated ACTH and cortisol responses to CRH as well as impaired suppression of ACTH and cortisol after administration of the synthetic glucocorticoid dexamethasone. Persons with an adrenal tumor overproducing cortisol have low circulating ACTH levels, little or no cortisol response to CRH or ACTH, and no suppression of cortisol levels after repetitive administration of large doses of dexamethasone.

Prolactin Axis

Prolactin is a 196 amino acid protein produced by lactotropes in the anterior pituitary gland. During pregnancy, this is also produced by decidual tissue. It bears a distant evolutionary resemblance to growth hormone. Thyrotropin-releasing hormone inhibits and dopaminergic stimuli promote release of prolactin. The major effect of prolactin is to promote mammary gland development and milk production. While prolactin has no major influence on growth, measurement of prolactin can help in discerning the locus of certain disorders that do influence growth. Prolactin levels can be measured in the resting state or after stimulation with TRH. Unlike the other anterior pituitary hormones, prolactin is normally subject to negative control by the hypothalamus.

Disorders

Interruption of the pituitary stalk disrupts hypothalamic signaling but leaves the systemic blood supply to the pituitary intact. When this communication is curtailed by vehicular trauma, inflammatory processes, or a deficit of hypothalamic tissue, circulating prolactin levels tend to be elevated. Prolactin levels are also high in persons with primary hypothyroidism, presumably because of increased secretion of TRH. Prolactin levels are low and fail to increase in response to TRH in persons with destruction of the pituitary and in those with genetic defects in certain transcription factors that are essential for the embryonic development and definitive function of lactotropes as well and somatotropes.

Insulin Axis

Insulin is produced by beta cells in the pancreatic islets of Langerhans. Increases in insulin secretion are prompted by rises in blood glucose. Somatostatin, produced by D cells in the islets, inhibits insulin release through a paracrine mechanism.

Disorders

Insulin appears to be important for normal fetal growth. The fetus with congenital insulin deficiency is short and underweight for length at birth. Conversely the fetus of a mother with poorly controlled diabetes overproduces insulin in response to high circulating glucose levels and tends to be longer and heavier than average at birth. Postnatally acquired diabetes commonly produces weight loss, but the interval between onset and diagnosis is usually too brief to have a discernible effect on stature.

Explanation: Distinguishing Between Hereditary and Acquired Disease

Timing

There is a tendency to think of disorders that make themselves known at or before birth as being genetic and those that appear later on as being acquired. This can be misleading. Environmental factors such as infections, toxins, and nutritional deficiencies can have effects on the developing fetus and thus result in congenital disorders. Conversely, the appearance of the first signs of a genetically determined disease may occur later in life. One example is the delayed and sequential emergence of anterior pituitary hormone deficiencies caused by human PROP1 mutations (see later).

Additional Laboratory or Radiological Findings

Most acquired hypothyroidism reflects thyroid destruction by an autoimmune attack on the thyroid gland. The presence of thyroiditis can be inferred by finding circulating antibodies to thyroidglobulin or thyroid peroxidase. Most congenital hypothyroidism is a reflection of agenesis (lack of development) or dysgenesis (abnormal development) of the thyroid gland. Radioisotopic imaging discloses small or misplaced (ectopic) thyroid glands. Despite human and animal models of mutations causing thyroid dysgenesis,[9] most instances are still thought to be due to as yet unidentified environmental influences. In congenitally hypothyroid infants, the finding of a large thyroid gland with avid iodine uptake generally indicates an autosomal recessive error in thyroid hormone synthesis.

Magnetic resonance imaging of the pituitary and hypothalamus helps in distinguishing hereditary from acquired disease. It is possible to recognize craniopharyngiomas (a developmental error of Rathke's pouch regression), optic nerve gliomas, or pituitary adenomas causing multiple pituitary hormone deficiency. The combination of a small anterior pituitary gland, a small infundibulum or pituitary stalk, and an ectopic posterior pituitary gland is a distinctive sign of congenital hypopituitarism. It may be accompanied by underdevelopment of the optic nerve and underdevelopment of the septum pellucidum and constitute septo-optic dysplasia or de Morsier's syndrome. While there have been some examples of multiple sibling involvement and homozygosity for a mutation in the HESX1 transcription factor gene, the majority of cases are still considered to be idiopathic.[10]

Genetic Considerations

The search for a genetic condition begins with a family history. Normal parents with two or more affected offspring suggests autosomal recessive inheritance. A similarly affected mother suggests autosomal dominant or X-linked dominant inheritance. A similarly affected father and an affected daughter is compatible with either autosomal dominant or X-linked dominant inheritance. Conversely an affected father and son combination implies autosomal dominant but excludes X-linked dominant inheritance. Transmission of a mutation in the mitochondrial gene takes place through the maternal line and can involve both males and females.

Now that it is possible to use molecular methods to detect mutations in specific growth-related genes, it is evident that the majority of persons with genetic disorders of growth do not have a positive family history of disease. For example, most cases of dominant mutations in the PIT1 pituitary transcription factor gene represent de novo mutations. In the case of autosomal recessive disorders, the first affected child does not have a family history of the disease. When family sizes are small, it is likely that the first affected child will remain the only affected child in that family. There should be a very high suspicion of autosomal recessive disease where there is parental consanguinity. There should also be a high suspicion of recessive disease in small, genetically isolated communities, where the parents are not closely related but both may carry the same mutation because of a founder effect.

For some disorders, the severity of involvement or the constellation of defects in different pituitary axes may strongly suggest a mutation in a particular gene. Over the past 20 years, mutations in the growth-hormone-releasing hormone receptor have been found responsible for some recessive forms of severe, isolated, GH deficiency. Other recessive and dominant forms of isolated GH deficiency have been traced to large mutations and small mutations in the GH-1 gene. The Laron syndrome of peripheral insensitivity to the action of GH has been explained by dominant and recessive mutations in the growth hormone receptor gene. The riddle of how mutation of a single gene can cause deficiency of several anterior pituitary hormones has been solved by discovery of transcription factors that direct embryonic development and mature function of the pituitary. This class of disorder includes dominant and recessive mutations of PIT1, recessive mutations of PROP1, recessive mutations of LHX3 and recessive mutations of HESX1.[11]

AN EXAMPLE OF DISORDERED GROWTH

To illustrate the application of principles underlying analysis of growth disorders, we consider the case of a young woman of extremely short stature who was originally described by Rosenbloom et al.[12]

Growth Phenotype: Severe Postnatal Growth Failure and Sexual Immaturity

"Maria" is a 23-year-old woman who lives in a small town in the Dominican Republic. Her height of 111.0 cm is 8.7 standard deviations (SD, or *Z*-scores) below the mean for her age and sex, using North American reference charts. It would be an average height for a 5-year-old girl. Her skeletal maturity is that of a 10-year-old. Her parents' heights are very close to the mean, so none of her height deficit can be explained by ordinary polygenic inheritance of stature. Very little detailed information is available about how she reached her current height. Her parents say that she was of normal size at birth and began to be noticeably small for age around 3 or 4 years old.

Her physical appearance is that of a little girl. Her BMI of 15.5 kg/m^2 is low for an adult, but about average for a 6-year-old. Her body proportions are similar to those of a 6-year-old, in that her span is slightly less than her height and her lower body segment is slightly less than her upper body segment. She does not have breast or pubic hair development and has not menstruated.

Hormonal Phenotype: Multiple Pituitary Hormone Deficiency

Assessment of the growth hormone axis began with measurement of IGF-1 and IGF-BP3 (Figure 10-2). The IGF-1 level was 8 ng/ml (normal range for adult females is 128–470 ng/ml) and the IGF-BP3 level was 0.4 mg/L (2–4 mg/L). A GH-BP level of 204 pg/ml was normal (66–306 pmol/L). Basal GH was <0.1 ng/ml

• BMI	15.5 kg/m^2	avg for HA
• GH BP	204 pmol/L	(66–306)
• IGF-1	8 ng/ml	(128–470)
• IGF-BP3	0.4 mg/L	(2–4)
• Basal GH	<0.1 ng/ml	(0.2–20)
• Stim GH	<0.1 ng/ml	(>10)

- A central defect in GH secretion
- GHRH stimulation would be needed to prove a defect at the pituitary level

FIGURE 10-2 The case study growth hormone axis.

(0.2–20 ng/ml) and did not rise into the detectable range with clonidine stimulation (>10 ng/ml). Stimulation with GHRH was not done, so the defect leading to GH deficiency could have resided at the hypothalamic or pituitary level.

Hypothyroidism was present (Figure 10-3), with a free T4 of 0.4 ng/dl (0.8–2.7 ng/dl). As in many cases of hypothyroidism, the total T3 level was in the normal range at 120 ng/dl (87–180 ng/ml). This probably reflects increased outer ring deiodination of thyroxine by peripheral tissues. An inappropriately low TSH level of 0.7 mU/ml (0.4–4.2 mU/ml) indicated that she had central hypothyroidism rather than failure of the thyroid gland. The low peak TSH level of 1.0 mU/ml (6–30 mU/ml) following TRH (Figure 10-4) supported a pituitary rather than a hypothalamic defect. Central hypothyroidism was accompanied by deficiency of prolactin, with a low basal level of 0.8 ng/ml (3.6–12 ng/ml) and a rise to only 6.0 ng/ml (10–60 ng/ml) following TRH.

The physical phenotype of sexual immaturity (Figure 10-5) was accompanied by an estradiol level of 4 pg/ml (>40 pg/ml), a low LH level of 0.25 IU/ml (1.7–20 IU/ml), and an FSH level of 0.75 IU/ml (1.4–40 IU/ml). Stimulation with LHRH would have been necessary to formally distinguish between a pituitary and a hypothalamic defect in gonadrotropin production.

- Low levels of thyroid hormones

– Free T4	0.4 ng/dl	(0.8–2.7)
– Total T3	120 ng/dl	(87–180)
– TSH	0.7 mU/L	(0.4–4.2)

- Low TSH response to TRH

– TSH peak	1.0 mU/L	(6–30)

- A central defect in the thyroid axis, probably at the level of the pituitary

FIGURE 10-3 The case study thyroid axis.

- Low Prl
  - Basal 0.8 ng/ml (3.6–12)
  - Post TRH 6.0 ng/ml (10–60)
- A partial defect in the prolactin axis, probably at the level o f the pituitary

FIGURE 10-4 The case study prolactin axis.

Serum cortisol was normal in a midafternoon sample. Stimulation with a physiologic dose of ACTH or sampling during an insulin stimulation test would be needed to recognize or exclude partial deficiency of ACTH. A normal 24-hour urinary volume, normal serum sodium, and a urine specific gravity of 1.025 excluded deficiency of antidiuretic hormone.

In summary, the hormonal phenotype in this individual included severe deficiency of GH, TSH, LH, and FSH, with less severe impairment of prolactin secretion. The pituitary adrenal axis and posterior pituitary function were normal. Central hypothyroidism was demonstrated to have a pituitary basis, and by implication, the defects in GH and gonadotropin secretion were also at the level of the pituitary.

Explanation: Homozygosity for Mutation in the PROP1 Gene

The clinical history suggested onset of disease during early childhood. There was no history of head trauma and no skin or bone manifestations of histiocytosis, a disorder that can cause acquired pituitary hormone deficiency. Imaging of the pituitary was limited to skull X rays. The sella turcica, a bony structure surrounding the pituitary, was slightly large but there were none of the suprasellar calcifications characteristic of craniopharygiomas.

- No menses by age 23
- No breast or pubic hair development
- Low estradiol level
  - E2 4 pg/ml (>20)
- Low basal LH and FSH
  - LH 0.25 IU/L (>1.7)
  - FSH 0.75 IU/L (>1.4)
- Central hypogonadism
- An LHRH stimulation test would help distinguish between hypothalamic and pituitary disease

FIGURE 10-5 The case study sex hormone axis.

Family history was informative. The subject had a sister who was only a year younger but was also the size of a 6-year-old. Furthermore, they had cousins who lived in a smaller town that was only a few miles away. Six of eight adult siblings in this family were also very short and sexually immature. They underwent testing and all proved to have similar hormonal phenotypes. The family history thus gave strong indications of an autosomal recessive disorder. The fact that they lived in nearby towns in an area that had a long history of settlement by the same families suggested that they might have a common ancestor and be homozygous for the same recessive mutation.

At about the time that these families were being studied at the levels of growth phenotype and hormonal phenotype, a report appeared describing a very attractive candidate gene. The PROP1 gene had been discovered in 1997 as the gene responsible for Ames dwarfism in the mouse.[13] Both the Ames mouse and the Snell mouse represent recessive disorders with deficiencies of GH, TSH, and prolactin. A pituitary transcription factor called PIT1 was characterized in 1998 as a nuclear protein that bound to both the GH and the prolactin disorder.[14] In 1990, the Snell mouse was found to have a mutation in this gene.[15] Subsequent studies identified PIT1 mutations in humans with multiple pituitary hormone deficiency.[11] Affected individuals had deficiencies of GH, TSH, and prolactin, but they entered puberty spontaneously. The initial description of PROP1 mutations in humans disclosed that affected individuals differed from those with PIT1 defects in that they had deficiencies of LH and FSH as well as GH, TSH, and prolactin.[16] Furthermore, the onset of pituitary hormone deficiencies was more delayed than with PIT1 mutations. Growth in infancy and early childhood was less profoundly impaired. Hence, there seemed to be a good match between the phenotypes observed in the Dominican families and those observed in the Canadian, Austrian, and German families described by Wu et al.[16]

The entire PROP1 gene was amplified by polymerase chain reaction and the three exons were sequenced. The Dominican patients were homozygous and their parents were heterozygous for a two base pair deletion in codon 99 of exon 2.[12] This deletion produces a shift of reading frame and predicts a truncated protein containing only 108 amino acids as compared to the 290 amino acids present in the normal protein. The mutant protein lacks part of the DNA-binding domain and all of the transcriptional activation domain. When the mutant protein was expressed in transfected cells, it was devoid of DNA-binding and transcriptional activation activities.[16] Our other studies have shown that this mutation, a one base pair deletion in codon 50, and a small number of other mutations in PROP1 account for multiple pituitary hormone deficiency in families from the United States, Jamaica, Brazil, among Hutterite communities in the United States and Canada, and in the cluster of families originally described by Hanhart on the isle of Krk in Croatia.[11,17] Mutations in PROP1 are particulary common in Poland, where they explain 37 of 52 (71%) of the cases of multiple pituitary hormone deficiency followed in a single clinic.[11] The high prevalence of one and two base pair deletions in PROP1 probably reflects hot spots for mutation at vulnerable points in the gene.

This example illustrates a logical sequence of investigation beginning with the observation of a single individual, proceeding through a description of growth, continuing with a dissection of hormone deficiencies, and culminating in discovery of a genetic observation. It portrays a particular breakdown in pituitary function as a common explanation for a rare phenotype that is widely distributed among different populations.

A COMPARISON OF GENETIC DISORDERS AT DIFFERENT POINTS IN THE GROWTH HORMONE AXIS

Deficiency of Growth Hormone and Other Anterior Pituitary Hormones

An Overview of Pituitary Transcription Factors

Anterior pituitary organogenesis involves invagination of Rathke's pouch with differentiation of five cell types that together produce six major hormones. Studies in the mouse indicate that the five species of hormone-producing cells derive from a single type of precursor and that this cell differentiation and expansion is directed by transcriptional activation proteins. These proteins contain DNA-binding domains that resemble those of the proteins directing segmentation in Drosophila. They are referred to collectively as *homeotic proteins* and their genes as *homeobox genes*. The genes that direct pituitary development have been given different names by the scientists who characterized them. Some are named for the tissues in which they were first discovered, others for the resemblance of their coding regions to related homeobox genes, and unlike nomenclature in Drosophila, very few are named for the phenotypes resulting from mutations. The location and timing of appearance of gene products is finely orchestrated. Mutations in one gene can alter the normal expression of other homeobox genes.

HESX1

HESX1 denotes a "homeobox gene expressed in embryonic stem cells." It is also expressed very early in the embryogenesis of the anterior pituitary, a fact which gave rise to the alternative name, RPX for Rathke's pouch homeobox. The gene is located on human chromosome 3p21.2, consists of four exons spanning a distance of 1.7kb and encodes a pair-domain DNA-binding protein of 175 amino acids. Expression is first detectable at embryonic day 8.5 in the mouse and it continues through day 15. Gene expression is widespread and includes the forebrain, Rathke's pouch, and the optic nerve. The HESX1 protein competes with PROP1 for the same class of DNA sites. When PROP1 is not expressed, the expression of HESX1 is prolonged.

In 1999, Dattani, Martinez-Barbera, and Thomas[10] reported on the phenotypes generated by transgenic inactivation of Hesx1 in the mouse and the consequences of a recessive loss of function mutation in humans. While most of the knockout mice died before birth, the few who survived had abnormalities of brain development, small or absent optic nerves, and a small anterior pituitary gland with a small or absent pituitary stalk. The mouse phenotype was an exaggerated version of the syndrome of septo-optic dysplasia (SOD) in humans. Of the many SOD patients screened for HESX1 mutations, two affected siblings showed homozygosity for an arginine to cysteine mutation at residue 15, located in the homeodomain. The mutant protein lacked DNA-binding activity. Subsequent studies have disclosed other HESX mutations in other individuals with optic nerve hypoplasia or GH deficiency. Additional cases are needed to clarify the growth and hormonal phenotypes associated with HESX1 mutations in humans.

PROP1

PROP1 has only one name, which stands for "prophet of Pit1."[13] The Ames mouse, which has a mutation in PROP1, does not produce normal amounts of PIT1 protein. PROP1 protein, first appearing in the mouse pituitary at around 10 days precedes and is a prerequisite for the appearance of PIT1 protein at around 14 days of fetal life. As mentioned in the discussion of our informative case, PROP1 defects result in combined deficiencies of growth hormone, TSH, prolactin, LH, and FSH. The hormone deficiencies generally appear in the temporal order GH, TSH, then LH and FSH.[18] It is not clear when prolactin deficiency develops. Some individuals enter puberty spontaneously and later regress from puberty, with a decline in LHRH-stimulated LH and FSH levels.[19] Some even develop ACTH deficiency with advancing age.[20] The size of the anterior pituitary gland, as defined by magnetic resonance imaging, may be small, medium, large, or extra large. A minority of persons with PROP1 defects may have greatly enlarged pituitary glands that subsequently regress, leaving a large and empty sella turcica. This sequence does not depend on the particular type of PROP1 mutation and it need not be seen in all of the affected members of a sibship. All of the human PROP1 mutations are autosomal recessive, and all seem to produce a more complete loss of protein function than the serine 83 to proline missense mutation in the Ames mouse. This protein retains about 20% of wild type DNA-binding and transactivation activities. The mouse model is more severe, in that the hormone deficiencies are evident from birth, but the human model is more severe, in that the hormonal phenotype extends to include gonadotropin and sometimes ACTH deficiencies. It is not known whether these differences are intrinsic to the two species or if similarly severe mutations in a mouse background would also result in gonadotropin deficiency.

PIT1

The PIT1 gene, also known as the POU1F1 gene, is expressed in the pituitary cells that make GH, TSH, and prolactin. It binds to promoter sites preceding the genes encoding these hormones and activates transcription. It also binds to promoter and upstream enhancer sites, so that PIT1 amplifies its own expression.[21] Expression begins around embryonic day 14, before the appearance of GH and prolactin but after appearance of TSH. PIT1-independent expression of TSH in a small population of thyrotropes is followed by PIT1-dependent expansion of a much larger population of thyrotropes. Mutations in the mouse PIT1 gene are responsible for dwarfism in the Snell and Jackson mouse models of hypopituitarism. In these mice and humans with PIT1 mutations, there is combined deficiency of GH, TSH, and prolactin. There is nearly complete absence of GH production, resulting in slight impairment of fetal growth and severe impairment of postnatal growth. Deficiency of TSH is much more variable, ranging from severe, congenital hypothyroidism to nearly normal thyroid function. In contrast to persons with PROP1 mutations, those with PIT1 mutations experience delayed but eventually complete sexual maturation. Anterior pituitary size, as assessed by magnetic resonance imaging, tends to be small or normal. Persons with PIT1 defects do not exhibit the phenomenon of pituitary enlargement followed by degeneration seen in some persons with PROP1 defects.

There are three general types of PIT1 mutations in humans. The first consists of recessive loss of function mutations. Single base substitutions that change crucial amino acids or introduce premature stop codons lead to loss of promoter-binding and transcriptional activation properties. There are also examples of dominant mutations. The most common is a substitution of tryptophan for arginine at position 271. The mutant protein has enhanced promoter binding but inhibits rather than activates transcription of target genes. A third, dominant, type of mutation also exhibits both gain and loss of function.[22] Substitution of glutamic acid for lysine and position 216 increases transcriptional activation at GH, beta-TSH, prolactin, and PIT1 promoters but dominantly inhibits action of wild-type protein at the upstream enhancer site for PIT1. Hypopituitarism seems to be caused by a failure of autoamplification of PIT1 expression.

LHX3

At a very early phase of embryonic development, LHX3 (also known as PLIM) is expressed in many types of neural tissue. Its expression is later restricted to the anterior pituitary. This protein may be needed for expression of HESX1, and it is known to bind to PIT1 protein. Mutations of human LHX3 have recently been recognized in two families.[23] In one, there was homozygosity for a missense mutation in the DNA-binding domain; in the second, there was homozygosity for a premature translational stop codon. In both families, the affected children had hypopituitarism with deficiencies of all the anterior pituitary hormones except for ACTH. The children also shared an unexpected physical finding. They were unable to turn their heads from side to side. There were no abnormalities of the cervical vertebrae, so this remains a puzzling but distinctive physical characteristic.

Isolated Deficiency of Growth Hormone

Persons with isolated growth hormone deficiency on a genetic basis show some impairment of prenatal growth and are, on average, about 1 SD below the mean for birth length. There is severe restriction of postnatal growth and lengths tend to be more than 4 SD below the mean by the first birthday. Tests of the thyroid, prolactin, adrenal, and gonadals axes are normal. In the two well-understood categories of hereditary GH deficiency, there is no GH response to indirect stimuli or to GHRH.

The Growth-Hormone-Releasing Hormone Receptor Gene

As for mutations in PIT1 and PROP1 gene, mutations in the GHRHR gene were first recognized in a mouse model of hypopituitarism. The *little* mouse has a glycine for aspartic acid substitution at position 60 that eliminates binding of GHRH to its receptor.[24] Several types of recessive loss of function mutations have been observed in humans. One involves introduction of a translational stop signal at position 72.[25,26] A second mutation, observed in a large Brazilian kindred,[27] leads to abnormal splicing of GHRHR mRNA and disruption of the translational reading frame. Neither of the truncated proteins can bind GHRH or take part in signaling. The mouse and human models of GHRHR mutation demonstrate that signal transmission through the GHRH receptor is essential for normal somatotrope development and function.

Growth Hormone Genes

The first molecular explanation for hypopituitarism involved recognition of a large deletion that included the GH-1 gene. It was found in members of a Swiss family.[28] The affected individuals had severe GH deficiency, showed a good initial response to GH treatment, and then developed high levels of antibodies to GH that interfered with subsequent growth. This phenomenon suggested that lifelong absence of GH had resulted in a lack of immune tolerance to the hormone. When extracted human GH was given by injection, the immune system reacted to it as a foreign protein. As other cases were reported, it appeared that this simple explanation was incomplete. Some children developed anti-GH antibodies and others did not. The antigenicity of a particular GH preparation is also important. Over the past 15 years, since the introduction of a much purer recombinant GH, development of anti-GH antiboidies in persons with GH-1 gene deletions has become much less frequent.

Deletions of different sizes may eliminate not only the GH-1 gene but other members of the GH and CS gene cluster. Loss of the CS pseudogene, the placental GH gene, and the two chorionic somatomammotropin genes, termed CS-1 and CS-2, does not add to the severity of the growth phenotype. Loss of all of these genes, with the exception of GH-1, does not produce any impairment of fetal or postnatal growth.[29]

There are other ways to lose GH-1 gene function. The literature contains reports of small deletions of 1 or 2 bp that alter reading frame and other mutations that introduce translational stop codons. Other mutations lead to abnormal splicing of GH-1 mRNA. The gene contains five exons with four intervening sequences. Mutations affecting the splice donor site in intron 4 cause a recessive form of GH deficiency. Mutations in intron 3 cause dominant GH deficiency.[30] Exon 3 is excluded from the spliced mRNA. There is no change of reading frame, but the smaller protein prevents expression of the protein product of the normal allele. This is thought to occur through interference with posttranslational processing.[31]

End Organ Resistance to the Action of Growth Hormone

The genetic disorders discussed up to this point all involve deficiency of GH, with or without deficiency of other anterior pituitary hormones. In the current category, GH is produced in normal or above normal amounts. Circulating GH levels are high and IGF-1 is low.

Growth Hormone Receptor Gene

There is no difference in physical appearance or growth phenotype between persons with GH deficiency and those with GH receptor defects. In both, intrauterine growth is nearly normal, but postnatal growth is severely compromised. Mutations of the GH receptor may be dominantly or recessively inherited. The recessive forms generally involve large deletions: frameshifts, nonsense, and missense mutations in the second through sixth exons of the 10 exon gene.[5] With a few notable exceptions, they produce a loss of GH-binding to the receptor. Measurement of the GH-binding protein, reflecting a circulating form of the extracellular portion of the receptor, depends on the binding of GH, so circulating GHBP levels are very low. Some mutations prevent dimerization of two receptor molecules around a single GH molecule. In these cases, circulating GHBP levels are normal. Other mutations result in production of a receptor lacking transmembrane and intracellular domains. The unanchored receptor is produced in excess and results in extremely high GHBP and GH levels.[32]

IGF-1 Gene

There is a single report of an individual with a defective IGF-1 gene.[6] He was homozygous for deletion of exons 3 and 4 of the gene. His growth phenotype included severe prenatal as well as postnatal growth retardation. His hormonal phenotype included high GH and GHBP levels. The level of IGHF-BP3 was also high but IGF-1 was undetectable.

GH-1 Gene

Gain of function mutations in the GH-1 gene result in a growth phenotype that differs from the phenotype of GH deficiency described in previous sections. Takahashi et al.[33] described a boy who was heterozygous for a single base substitution that changed the arginine at position 77 to a cysteine. As in the patient with an IGF-1 deletion, the growth phenotype involved severe limitations of prenatal and postnatal growth. The mutant GH bound to GHBP with an affinity several times greater than that of normal GH. It also bound to the GH receptor on target cells, but did not activate the JAK-STAT pathway involved in intracellular signal transduction. This naturally occurring GH antagonist produced very severe intrauterine growth retardation, to a degree that matched that produced by IGF-1 gene deletion. The explanation for such a profound effect on fetal growth is unclear. It is possible that more than one type of receptor is capable of stimulating production of IGF-1. This second receptor may the prolactin receptor, which recognizes human GH as well as prolactin and chorionic somatomammotropin. In this case, the effect of an antagonistic GH may be attributable to blockade of both the GH and the prolactin receptors.

CONCLUSION

This chapter looks at endocrine disorders of growth from definition of the growth phenotype, through delineation of the possible variations in the level of circulating hormones, to descriptions of some of the various genetic lesions that can account for altered patterns of growth. The principles of assessment of growth through fetal life, infancy, childhood, and adolescence are well established. The catalogue of hormones and the strategies for measuring them are changing at a rapid rate. Even though the material discussed in this chapter is complex, a number of components have been omitted. These include leptin, a hormonal product of fat cells that exerts feedback control at the level of the pituitary and hypothalamus, and Ghrelin, a growth hormone secretagogue produced in the stomach, placenta, and hypothalamus.[34] Further clarification of these hormonal pathways will pave the way for recognizing new categories of genetic and acquired disorders of growth.

REFERENCES

1. Mayo KE. Molecular cloning and expression of a pituitary-specific receptor for growth hormone-releasing hormone. Mol Endocrinol. 1992;6:1734–1744.
2. Butler AA, LeRoith D. Minireview: Tissue-specific versus generalized gene targeting of the igf1 and igf1r genes and their roles in insulin-like growth factor physiology. Endocrinol. 2001;142:1685–1688.
3. Laron Z, Pertzelan A, Mannheimer S. Genetic pituitary dwarfism with high serum concentration of growth hormone—A new inborn error of metabolism? Isr J Med Sci. 1966;2:152–155.
4. Godowski PJ, Leung DW, Meacham LR, Galgagni JP, Hellmiss R, Keret R, et al. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron type dwarfism. Proc Natl Acad Sci U S A. 1989;86:8083–8088.
5. Parks JS, Brown MR, Faase ME. The spectrum of growth hormone insensitivity. J Pediatr. 1997;131:S45–S50.
6. Woods, KA, Camacho-Hubner C, Savage, MO, Clark AJL. Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. N Engl J Med. 1996;335:1363–1367.
7. de Zegher F, Pernasetti F, Vanhole C, Devlieger H, Van den Berghe G, Martial JA. The prenatal role of thyroid hormone evidenced by fetomaternal Pit-1 deficiency. J Clin Endocrinol Metab. 1995;80:3127–3130.
8. Brucker-Davis F, Skarulis MC, Grace MB, Benichou J, Hauser P, Wiggs E, et al. Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health Prospective Study. J Clin Endocrinol Metab. 1995;123:572–583.

9. Macchia PE, Lapi P, Krude H, Pirro MT, Missero C, Chiovato L, et al. PAX8 mutations associated with congenital hypothyroidism caused by thyroid dysgenesis. Nat Genet. 1998;19:83–86.
10. Dattani M, Martinez-Barbera J-P, Thomas PQ. Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and in mouse. Nat Genet. 1998;19:125–133.
11. Parks JS, Brown MR, Hurley DL, Phelps CJ, Wajnrajch MP. Heritable disorders of pituitary development. J Clin Endocrinol Metab. 1999;84:4362–4370.
12. Rosenbloom AR, Almonte AS, Brown MR, Fisher DA, Baumbach L, and Parks JS. Clinical and biochemical phenotype of familial anterior hypopituitarism from mutation of the PROP1 gene. J Clin Endocrinol Metab. 1999;84:50–57.
13. Sornson MW, Wu W, Dasen JS, Flynn SE, Norman DJ, O'Connell SM, et al. Pituitary lineage determination by the Prophet of Pit-1 homeodomain factor defective in Ames dwarfism. Nature. 1996;384:327–333.
14. Mangalam HJ, Albert VR, Ingraham HA, Kapiloff M, Wilson L, Nelson C, et al. A pituitary POU domain protein, Pit-1, activates both growth hormone and prolactin promoters transcriptionally. Genes Dev. 1989;3:946–958.
15. Li S, Crenshaw EB III, Rawson EJ, Simmons DM, Swanson LW, Rosenfeld MG. Dwarf locus mutants lacking three pituitary cell types result from mutations in the POU-domain gene Pit-1. Nature. 1990;347:528–533.
16. Wu W, Cogan JD, Pfaffle RW, Dasen JS, Frisch H, O'Connell SM, et al. Mutations in PROP1 cause familial combined pituitary hormone deficiency. Nat Genet. 1998;18:147–149.
17. Krzisnik C, Kolacia Z, Brown MR, Battelino T, Parks JS, Laron Z. The "Little People" of the Island Krk-Revisited: etiology of hypopituitarism. J Endocrine Genet. 1999;1:9–19.
18. Deladoey J, Fluck C, Buyukgebiz A, Kuhlmann BV, Eble A, Hindmarsh PC, et al. "Hot spot" in the PROP1 gene responsible for combined pituitary hormone deficiency. J Clin Endocrinol Metab. 1999;84:1645–1650.
19. Fluck C, Deladoey J, Rutishauser K, Eble A, Marti U, Wu W, et al. Phenotypic variability in familial combined pituitary hormone deficiency caused by a PROP1 gene mutation resulting in the substitution of arg-cys at codon 120 (R120). J Clin Endocrinol Metab. 1998;83:3727–3734.
20. Pernasetti F, Toledo SP, Vailyev VV, Hayashida CY, Cogan JD, Ferrari C, et al. Impaired andreocorticotropin-adrenal axis in combined pituitary hormone deficiency caused by a two-base pair deletion (301-302delAG) in the prophet of Pit-1 gene. J Clin Endocrinol Metab. 2000;85:390–397.
21. Rhodes SJ, Chen R, DiMattia GE, Scully KM, Kalla KA, Lin SC, et al. A tissue-specific enhancer confers Pit-1-dependent morphogen inducibility and autoregulation on the Pit-1 gene. Genes Dev. 1993;7:913–932.
22. Cohen LE, Zanger K, Brue T, Wondisford FE, Radovick S. Defective retinoic acid regulation of the Pit-1 gene enhancer: A novel mechanism of combined pituitary hormone deficiency. Mol Endocrinol. 1999;13:476–484.
23. Netchine I, Sobrier ML, Krude H, Schnabel D, Maghnie M, Marcos E, et al. Mutations in LHX3 result in a new syndrome revealed by combined pituitary hormone deficiency. Nat Genet. 2000;25:182–186.
24. Godfrey P, Rahal JO, Beamer WG, Copeland NG, Jenkins NA, Mayo KE. GHRH receptor of little mice contains a missense mutation that disrupts receptor function. Nat Genet. 1993;3:227–232.
25. Wajnrajch MP, Gertner JM, Harbison MD, Caua SC Jr, Leibel RL. Nonsense mutation in the human growth hormone-releasing hormone receptor causes growth failure analogous to the little (lit) mouse. Nat Genet. 1996;12:88–90.
26. Mahareshi HG, Silverman BL, Dupuis J, Baumann G. Phenotype and genetic analysis of a syndrome caused by an inactivating mutation in the growth hormone-releasing hormone receptor: Dwarfism of Sindh. J Clin Endocrinol Metab. 1998;83:4065–4073.
27. Hayashida CY, Gondo RG, Ferrari C, Toledo SP, Salvatori R, Levine MA, et al. Familial growth hormone deficiency with mutated GHRH receptor gene: Clinical and hormonal findings in homozygous and heterozygous individuals from Itabaianinha. Euro J Endocrinol. 2000;142:557–563.
28. Phillips JA 3rd, Hjelle BL, Seeburg PH, Zachmann M. Molecular basis for familial isolate growth hormone deficiency. Proc Natl Acad Sci U S A. 1981;78:6372–6375.

29. Parks JS. Molecular pathology of growth hormone deficiency. In: Thakker RV (ed). Molecular Genetics of Endocrine Disorders. London: Chapman and Hall Medical, 1997:17–38.
30. Cogan JD, Phillips JA III, Schenkman SS, Milner RD, Sakati N. Familial growth hormone deficiency: A model of dominant and recessive mutations affecting a monomeric protein. J Clin Endocrinol Metab. 1994;70:1261–1265.
31. Lee MS, Wajnrajch MP, Kimm SS, Plotnick LP. Autosomal dominant growth hormone (GH) deficiency type II: the Del32-71-GH deletion mutant suppresses secretion of wild-type GH. Endocrinol. 2000;141:863–890.
32. Woods KA, Fraser NC, Postel-Vinay MC, Savage MO, Clark AJ. A homozygous splice site mutations affecting the intracellular domain of the growth hormone (GH) receptor resulting in Laron syndrome with elevated GH-binding protein. J Clin Endocrinol Metab. 1996;81:1683–1685.
33. Takahashi Y, Kaji H, Okimura Y, Goji K, Abe H, Chihara K. Short stature caused by a mutant growth hormone. N Engl J Med. 1996;334:432–436.
34. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from the stomach. Nature. 1999;402:656–660.

11

GENETICALLY DETERMINED GROWTH DISORDERS

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INTRODUCTION

In this chapter we will discuss disorders of growth with a genetic etiology where the effect on growth is not mediated through the classical endocrine growth regulatory system. Gene defects that lead to endocrine dysfunction are discussed in Chapter 10.

There are far too many disorders in this group for this chapter to attempt to be exhaustive. The approach will be to illustrate some of the major genetic mechanisms that lead to growth disorders, where possible using examples that are among the more common. Mostly, the emphasis will be on the single gene defect disorders, but first we discuss some growth disorders associated with major chromosomal abnormalities. In all these conditions (single gene or larger chromosomal defects), the resulting phenotype often includes other clinical problems in addition to abnormal growth. As such they often form a syndrome; that is, a group of clinical abnormalities that are generally grouped together but may not all be manifest in any one child. This is rather different to the more specific effects seen in children with genetic disorders of the endocrine system.

The chromosomal abnormality may be an additional chromosome (a whole or a fragment; trisomy), a deletion (a whole or a fragment), or a translocation (where part of one chromosome is fused with another). In the last case, if there is no net gain or loss of genetic material, then the translocation is said to be balanced and is usually not associated with a clinical abnormality. On the other hand, if there is loss or gain of genes, there is likely to be a phenotypic effect.

The separation into major chromosomal rearrangements and single gene defects becomes increasingly difficult with the discovery of increasing numbers of syndromes associated with submicroscopic deletions and translocations involving only a few genes. We discuss this in more detail later. A third group of conditions deserves mention: There is an increasing group of growth disorders in which an alteration in gene expression involves the group of imprinted genes whose expression is dependent on the parent of origin.

A few terminological conventions need stating. When referring to a gene, the name is given in italics and in humans usually all in capitals, such as *FGFR3* (see later); its encoded protein may be stated in full but more often is abbreviated and in roman capitals, such as FGFR3. Mutations, where possible, are referred to as, for example, Lys123Arg, where Lys stands for lysine in the normal or wild-type protein, 123 is the amino-acid position in the protein, and Arg (arginine) is the mutant amino acid. If the DNA mutation is referenced, it is given as, for example, C456G, where C (cytosine) is the wild-type nucleotide at position 456 in the gene and G (guanine) is the mutant nucleotide. Other frequently used mutation nomenclature is listed in Table 11-1.

MAJOR CHROMOSOMAL ABNORMALITIES

Down Syndrome

One of the more common chromosomal disorders with an incidence of 1 in 700 live births, Down syndrome is more usually thought of as a combination of severe mental retardation, characteristic facial features, and often major cardiac and gastrointestinal abnormalities, rather than as a growth disorder.[1] A more complete list of the features of Down syndrome is given in Table 11-2. However, short stature is a consistent feature, with mean adult height of 145 cm (female) and 158 cm (male) (Styles et al., personal communication). In 94% of Down syndrome patients,

TABLE 11-1 Nomenclature of More Common Forms of Gene Mutations

Term	Nature of Mutation	Effect on Protein Product
Missense	Single nucleotide change	Amino-acid substitution
Nonsense	Single or multiple nucleotide change, including deletions or insertions leading to a frameshift and premature STOP codon	Truncated protein
Splice site	Use of an unexpected splice site during gene expression with loss or gain of the whole or part of an exon	Usually quite major alteration of protein

TABLE 11-2 Clinical Features of Down Syndrome

Stature:

Short stature

Neurologic:

Mental retardation
Alzheimer disease
Hypotonia

Head and Neck:

Flat facial profile
Brachycephaly
Upslanting palpebral fissures
Epicanthal folds
Brushfield's spots
Protruding tongue
Small ears
Folded helix
Conductive hearing loss

Skeletal:

Hypoplastic iliac wings
Shallow acetabulum
Atlanto-axial instability
Short, broad hands
Fifth finger midphalanx hypoplasia
Single transverse palmar (Simian) crease
Joint hypermobility

Endocrine:

Hypothyroidism

Ectoderm:

Excess nuchal skin

Cardiovascular:

Congenital heart defect
Atrioventricular canal

Gastrointestinal:

Duodenal stenosis or atresia
Imperforate anus
Hirschsprung disease

Hematologic:

Leukemoid reactions

Neoplasia:

Leukemia (both ALL and AML)
Acute megakaryocytic leukemia

Miscellaneous:

Meiotic origin > 95% maternal, mostly meiosis I
Increased recurrence risk with parental translocation
Incidence, 1 in 650–1000 live births

Inheritance:

Not Mendelian
Full trisomy 21, 94%
Mosaic trisomy 21, 2.4%
Translocation 21, 3.3%

there is a total chromosome count of 47 with trisomy of chromosome 21; in the remainder, there is a translocation of the extra chromosome 21 onto another chromosome, usually 14. The extra chromosome arises by nondisjunction in meiosis I, and this is nearly always maternal in origin; incidence rises dramatically with increasing maternal age.

Much time and effort have been spent in attempts to identify the critical regions of chromosome 21 that are responsible for the syndrome. While some genes have been identified that might be associated with particular aspects of the syndrome (e.g., *DSCR1*,[2] which is highly expressed in the brain and heart), it seems increasingly likely that Down syndrome is a contiguous gene defect involving multiple regions of the chromosome.

Turner Syndrome

In its classical form, this syndrome is associated with monosomy of chromosome X (45X), although there are many variants, some with mosaicism and some with more subtle structural rearrangements of one of the X chromosomes.[1] Short stature is a major feature of the condition, whatever the chromosomal abnormality, but there are many other features, such as ovarian dysgenesis, congenital heart and renal disease, and other morphological abnormalities (Table 11-3). Many of the morphological abnormalities are probably secondary to lymphatic system problems in fetal life.

TABLE 11-3 Clinical Features of Turner Syndrome

Stature:

Low birth weight
Short stature

Neurologic:

Verbal IQ > performance IQ
Cognitive deficits
Immature personality

Head and Neck:

Brachycephaly
Epicanthal folds
Low-set ears
Conductive or sensorineural hearing loss
High-arched palate

Skeletal:

Cubitus valgus
Short metacarpals, usually IV
Fifth finger midphalanx hypoplasia
Decreased carpal arch

Endocrine:

Hypothyroidism

Ectoderm:

Pigmented naevi
Lymphedema
Hypoplastic nails

Cardiovascular:

Coarctation of the aorta or ventricular septal defect

Gastrointestinal:

Telangiectasia

Renal:

Horseshoe kidneys
Unilateral renal aplasia

While in some ways the short stature would appear to have a multigenic etiology, like Down syndrome, it now seems more likely that a single-gene defect causes the major part of the abnormal growth pattern. At the tip of the short arm of chromosome X (p22.3) is a region that is homologous with a similar region of the Y chromosome and behaves like an autosome at meiosis (the so-called pseudoautosomal region 1; *PAR1*). Located in that region is the gene *SHOX*, which has been shown to be implicated in some other short-stature syndromes.[3,4] When there is haploinsufficiency for this region (i.e., deletion of gene or genes on one of the chromosome pair), short stature results; and this is probably the explanation of most if not the entire growth pattern in Turner syndrome, where loss of this region is almost always seen. Thus, while the varied dysmorphic and other features of Turner syndrome are due to major chromosomal loss or rearrangement, it is increasingly likely that the short stature component is more correctly described as a single-gene defect.

The actual function of *SHOX* (Short stature HOmeoboX-containing gene) and how its haploinsufficiency causes short stature are still unclear. The homeobox genes share a region of approximately 60 nucleotides that are highly conserved, even across species. The equivalent region of the encoded protein is involved in binding DNA, and these gene products are involved in the regulation of gene transcription. *SHOX* itself is highly expressed in osteogenic tissues, and it is therefore not surprising that it is involved in bone growth.

SINGLE-GENE DEFECTS

There are both dominantly and recessively inherited single-gene disorders that affect growth, but the former are much more common. In a number of these conditions, the relevant gene is known, although in a great number, this is not so. In some of these syndromes, linkage studies have mapped the condition to a particular chromosome or region of a chromosome, but as yet nothing more is known. Even where the gene has been identified, it is not always possible to understand the function of that gene and its protein product and how mutation leads to the clinical phenotype. In what follows, examples of dominant and recessive disorders are discussed.

Achondroplasia and Hypochondroplasia

These two dominantly inherited growth disorders have phenotypes that have some overlap but still a distinct difference even though they involve the same gene, *FGFR3*. They are the more common two members of a larger family that includes thanatophoric dysplasia (a severe, lethal short-limb dysplasia syndrome) and SADDAN dysplasia (similar to thanatophoric dysplasia but not necessarily lethal and associated with a characteristic skin pigmentation). The latter are also caused by *FGFR3* mutations.[5]

Clinical Description

Achondroplasia is the most common form of human dwarfism and occurs in 1 in 15,000–40,000 live births. It is autosomal dominant with complete penetrance, and its main features are severe short-limbed dwarfism, with tibial bowing, a large bossed head, depressed nasal bridge, lumbar lordosis, and trident hands.[6] A more comprehensive list of features is given in Table 11-4. X rays are characteristic, with shortening of long bones with squared-off iliac wings, the sacrosciatic notch is narrow, and there is distal reduction of the vertebral interpedicular distance. Histopathology shows a defect in the maturation of the growth plates of long bones.

Hypochondroplasia is also autosomal dominant. It is generally milder than achondroplasia, although the degree of short stature is very variable.[7] There is usually lumbar lordosis, but the head is normal and there is no tibial bowing, although the limbs are short. It can be distinguished from achondroplasia on clinical and radiological grounds. The pelvis is normal. The spinal canal narrows in its caudal portion, as in achondroplasia. The fingers are short but the hand is not of the trident type. Table 11-5 gives a more comprehensive list of clinical features.

TABLE 11-4 Clinical Features of Achondroplasia

Stature:

Short-limb dwarfism identifiable at birth
Mean male adult height, 131 cm
Mean female height, 124 cm

Head and Neck:

Frontal bossing
Megalencephaly
Foramen magnum stenosis
Midface hypoplasia
Low nasal bridge
Recurrent otitis media in infancy and childhood
Conductive hearing loss

Respiratory:

Upper airway obstruction

Skeletal:

Lumbar kyphosis in infancy
Exaggerated lumbar lordosis during childhood and adulthood
Congenital spinal stenosis due to short pedicles, especially lumbar
Progressive interpediculate narrowing in lumbar spine
Limited elbow and hip extension
Generalized joint hypermobility
Rhizomelic shortening
Trident hand
Brachydactyly
Short femoral neck
Metaphyseal flaring
Dysplastic ilium with narrow sacroiliac groove
Flat rooted acetabulae
Bowing of legs

Neurologic:

Hydrocephalus, occasional
Hypotonia in infancy and early childhood
Brain stem compression
Delayed motor development

Inheritance:

Autosomal dominant with complete penetrance
80% cases new mutations
Paternal age effect

TABLE 11-5 Clinical Features of Hypochondroplasia

Growth:

Short-limb dwarfism identifiable during childhood
Final height, 125 to 160 cm

Head and Neck:

Macrocephaly
Mild frontal bossing
Normal to mild midface hypoplasia

Skeletal:

Variable lumbar lordosis
Progressive narrowing of interpediculate distance in the lumbar vertebrate
Short, squared ilia
Shortened limbs
Short tubular bones with mild metaphyseal flare
Limited extension at elbows
Genu varum
Bowleg
Lack of trident hand helps distinguish it from achondroplasia
Brachydactyly

Neurologic:

Occasional mental retardation

Miscellaneous:

Genetic heterogeneity, some patients not linked to FGFR3

Inheritance:

Autosomal dominant

FGFR3

The gene responsible for both achondroplasia and hypochondroplasia is *FGFR3*, on chromosome 4p16.3, which encodes the protein fibroblast growth factor receptor 3 (*FGFR3*). This protein is one of a family of at least three related receptor proteins that act as receptors for a number of fibroblast growth factors, which seem to have great importance in cell growth and signaling. Its schematic structure is shown in Figure 11-1. Mutations in *FGFR3* have now been associated with a number of skeletal disorders, including achondroplasia and hypochondroplasia.[5]

This receptor has a number of noteworthy features. All the FGF receptors have a well-conserved structure. There are three immunoglobulinlike loops (Ig I–Ig III) in the extra cellular domain with disulfide bonds maintaining the loop structure. A sequence of acidic amino acids lies between Ig I and Ig II (the acid box). There is a transmembrane domain and the intracellular domain containing ATP binding and catalytic sites. Ig III is actually encoded by three exons: exon IIIa encodes the amino-terminal half of the loop with exons IIIb or IIIc encoding the carboxy-terminal portion. This alternative splicing alters ligand specificity and tissue-specific expression. In bones, Ig III is almost exclusively encoded from exons IIIa and IIIc.

Disease-Related Mutations

In achondroplasia, there is remarkable homogeneity of the responsible mutations. They all occur in the transmembrane domain (see Figure 11-1), and the vast majority involve nucleotide 1138, with in the majority of cases a G-to-A transition

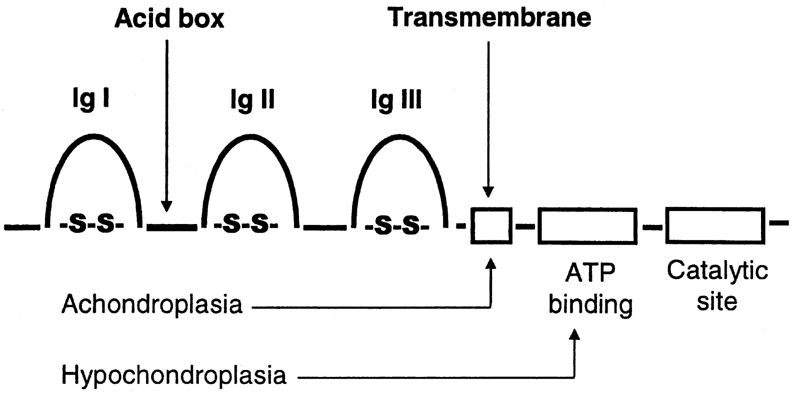

FIGURE 11-1 Schematic representation of FGFR protein. The three Ig-like domains are closed by disulphide bridges. The principal sites for mutations causing achondroplasia and hypochondroplasia are indicated.

but with occasional cases having a G-to-C transversion. Both these mutations lead to the same amino-acid substitution; namely, Gly380Arg. Both mutations create a new restriction site but are responsive to different restriction enzymes, so that screening for the two mutations is a relatively straightforward exercise.

The striking homogeneity of the achondroplasia-causing mutations in *FGFR3* has been confirmed in multiple populations including the United States, Sweden, the United Kingdom, China, and Japan (reviewed in Vago, Francomano, and Wilkin[5]). These observations and the relatively high incidence of achondroplasia imply that nucleotide 1138 of *FGFR3* is one of the most prone to mutation in the human genome. In sporadic cases of achondroplasia, the spontaneous new mutation is always on the paternally derived chromosome, suggesting an advanced paternal age effect and that factors influencing DNA replication or repair during spermatogenesis may predispose to the occurrence of the achondroplasia mutation.[8]

In hypochondroplasia, the principal mutation site lies in the ATP-binding region of the intracellular domain of *FGFR3.* C1620A and C1620G transversions resulting in an Asn540Lys substitution have been reported, as has a Ile538Val substitution.[9] However, in many reported cases, mutations are not found in this region; and in many cases, linkage studies have not shown linkage to chromosome 4p16.3. These observations support a view that hypochondroplasia is a much more clinically and genetically heterogeneous condition.

Outcomes of the *FGFR3* Mutations

Achondroplasia and hypochondroplasia mutations have been studied extensively. Targeted disruption (i.e., complete knockout) of *FGFR3* in mice causes enhanced bone growth of long bones and vertebrae, suggesting that FGFR3 negatively regulates bone growth. Therefore, the achondroplasia family of mutations could be interpreted as gain-of-function mutations that activate the negative growth regulation exerted by the FGFR3 signaling pathway. In the normal situation, ligand-binding is required to activate the FGFR pathways, but the point mutations described in achondroplasia and hypochondroplasia seem to initiate a ligand independent or constitutive activation that initiates the postreceptor cascade, leading to disrupted cell growth.

Diastrophic Dysplasia

Diastrophic dysplasia is a recessive disorder that, like those just described, is part of a spectrum of disorders associated with mutations in a single gene, *DTDST*.

Clinical Description

Diastrophic dysplasia (DTD) is a severe, short-limb dysplasia characterized by scoliosis, a form of clubbed foot bilaterally, malformed ears with calcification of the cartilage, premature calcification of the costal cartilages, and cleft palate in some cases (a more complete list is given in Table 11-6).[10] Particularly characteristic is the "hitchhiker" thumb due to deformity of the first metacarpal. A narrow chest and small lower jaw may lead to respiratory difficulties that can be fatal. It is particularly common in Finland, where growth data on 121 Finnish patients with DTD were collected.[11] Median adult height was 136 cm for males and 129 cm for females. Growth failure was progressive, partly because of an absent or

TABLE 11-6 Clinical Features of Diastrophic Dysplasia

Growth:

Short-limb dwarfism identifiable at birth

Head and Neck:

Normocephaly
Neonatal cystic lesions of the pinnae
Hypertrophic auricular cartilage
Ossified pinnae
Cleft palate

Thorax:

Costal cartilage calcification

Spine:

Cervical subluxation
Kyphosis
Scoliosis

Limbs:

Hitchhiker thumb
Symphalangism of proximal interphalangeal joints
Brachydactyly
Bilateral club foot

Inheritance:

Autosomal recessive

weak pubertal growth spurt. Radiologically, there is marked shortening of the first metacarpal, varying lengths of the metacarpals, and abnormal calcification of other hand bones. The dysplasia is associated with mutations in the diastrophic dysplasia sulfate transporter (*DTDST*),[12] which is also associated with two more severe dysplasias, atelosteogenesis type 2 (AO2) and the lethal condition achondrogenesis type 1B (ACG1B).

DTDST

The gene *DTDST* encodes a novel sulfate transporter protein, diastrophic dysplasia sulfate transporter (DTDST). Impaired function of this product leads to undersulfation of proteoglycans in the cartilage matrix, leading to disorganized cartilage and bone formation. The activity profile of sulfate transport in the growth plate chondrocytes, when studied in the extracellular presence of various anions, is dominantly dependent on the DTDST system. Undersulfation of proteoglycans significantly impairs the growth response of the cells to fibroblast growth factor, consistent with a role for DTDST in endochondral bone formation.

Disease-Related Mutations

Several point mutations have been identified, but strikingly not in the important Finnish population. Examples are a single base deletion at codon 575 (AAG → AG) and a similar deletion at codon 661 (ACA → AC). This results in a frame shift, as the deleted DNA sequence is not an exact multiple of three nucleotides, so that subsequent codons of three nucleotides each assume different combinations. A common outcome of this situation is that one such altered codon becomes TGA, TAG, or TAA, which are the signal to stop translation (the STOP codon) with consequent truncation of the protein.

The puzzle of the Finnish patients was resolved in 1999, when a splice-site mutation was discovered in a previously undescribed 5' untranslated exon of *DTDST* (i.e., an exon upstream of exon 1 and transcribed but not subsequently translated into protein; these exons often have a regulatory role).[13] This would be expected to severely disrupt gene expression and lead to greatly reduced protein synthesis. The mutation is now recognized to be causal for the majority of the Finnish families and constitutes a "founder effect."

Outcomes of *DTDST* Mutations

Mutations in the *DTDST* have been associated with a family of chondrodysplasias (see earlier) with a correlation between the nature of the mutations and the clinical phenotype. Studies of the degree of proteoglycan undersulfation in vivo in 12 patients with sulfate-transporter chondrodysplasias has cast considerable light on their pathophysiology. The amount of nonsulfated disaccharide (a major constituent of proteoglycans) was elevated in patients' samples, the highest amount being present in ACG1B patients (the most severe phenotype), indicating that undersulfation of chondroitin sulfate proteoglycans occurs in cartilage in vivo and is correlated with the clinical severity.

GENOMIC IMPRINTING AND UNIPARENTAL DISOMY

Until the 1980s, each member of the 22 pairs of autosomes, 1 originating from each parent, was thought to be equivalent, carrying out similar functions in duplicate. However, animal experiments and analysis of a number of human diseases have revealed that this assumption is not true. Some genes are expressed only from either the paternally or maternally inherited copy (i.e., “genomic” or “gametic” imprinting). These surprising discoveries forced classical Mendelian genetics to undergo revision and presented a genetic paradox. By silencing one allele of certain genes, mammals discarded the advantages of diploidy in exchange for a state of haploinsufficiency. How genomic imprinting benefits mammals is still not fully understood; and here we concentrate on the evidence for its existence, its association with uniparental disomy, and its involvement in intrauterine and postnatal growth.

Genomic Imprinting

In both mouse and man, disruption of the expression of imprinted genes has been linked to phenotypes associated with growth. The normal pattern of imprinted genes in some chromosomal regions can be altered by several different mechanisms: the inheritance of a chromosome pair from one parent (uniparental disomy, see later), the loss of one of the parental copies (a deletion), or a localized mutation in an imprinted gene or control domain. Although it is now clear that the loss of genomic imprinting is relevant to human disease, the initial evidence for the phenomenon came from elegant mouse experiments.

In the early 1980s, a series of experiments in mice provided the first evidence of the nonequivalent expression of paired genes.[14] Using sophisticated pronuclear transplantation experiments, maternal or paternal pronuclei were removed from and then reintroduced into zygotes, producing embryos with either maternal or paternal genomes. Embryos containing only maternal chromosome pairs are termed *gynogenetic* and those with only paternal chromosome pairs, *androgenetic*. Not surprisingly, neither zygote was viable, but there were both morphological and developmental differences between the two. The gynogenetic fetuses had poorly developed placentas but visible embryos, whereas androgenetic development was exclusively extraembryonic. These studies suggested that paternally expressed genes regulate placental development, whereas other, maternally expressed genes are involved with embryonic development.[15,16]

One of the best examples of abnormal development as a result of genomic imprinting in humans is seen in the complete hydatidiform mole.[17] This abnormal conceptus is composed entirely of fluid containing trophoblast tissue with no fetal tissue, and the genotype is entirely paternal in origin. Although such a genotype is incompatible with fetal survival, it still produces extraembryonic tissue and is reminiscent of the mouse androgenotes. Triploid conceptuses also show imprinting effects. Those with an extra paternally derived chromosome set usually have a large overgrown placenta and fetal intrauterine growth retardation (IUGR), whereas those with two copies of the maternal genome abort early with a poor, underdeveloped placenta.[18]

Uniparental Disomy

Another phenomenon that involves and exposes imprinting effects is that of uniparental disomy (UPD), which occurs when a pair of homologous chromosomes is inherited from the same parent. Several mechanisms could give rise to uniparental disomy, but the most likely is "trisomic rescue," involving the loss of a supernumerary chromosome from a trisomic conceptus, leaving two homologues from the same gamete.[19] High rates of aneuploidy in gametes (up to 50% in oocytes but only 5% in spermatozoa) suggest that maternal UPD could be fairly common, with trisomic rescue being the most likely mechanism.[20] As the karyotype appears normal, UPD detection requires DNA marker analysis.

The significance of UPD is twofold: the introduction of recessive gene disorders from the carrier parent and the potential disturbance of the expression of imprinted genes. The former situation may arise if two circumstances occur. First, the parent who will ultimately contribute both copies of a particular chromosome is a carrier for a recessive gene on that chromosome. And, second, the child inherits two copies of the chromosome with the recessive gene. Then the child ends up with two copies of the recessive gene and is therefore homozygous for that gene and will be likely to show the relevant clinical phenotype. This has been seen in several recessive disorders of which the best known is cystic fibrosis.

Uniparental disomy can lead to phenotypic effects when imprinted genes are involved. For example, if a maternally expressed gene is carried on a particular chromosome, when a child has maternal UPD of that chromosome, then two active copies of the gene are inherited and an overdose effect may be seen. In contrast, if the same gene was involved in paternal UPD, two inactive copies are inherited and the gene is effectively deleted.

Human Imprinting Disorders Affecting Growth

Examples of human UPDs associated with growth or endocrine phenotypes are listed in Table 11-7; these all probably involve imprinted genes. One of the best known of these conditions is the Beckwith-Wiedemann syndrome (BWS). The cardinal features of BWS are pre- and postnatal overgrowth, hemihypertrophy, exomphalos, and macroglossia.[21] There is often neonatal hypoglycemia with hyperinsulinemia associated with β-cell hyperplasia. There is also an increased risk of developing embryonal tumors, particularly Wilms'. It is associated with biallelic overexpression of *IGF2*, which is normally expressed only from the paternal allele. This can occur by paternal duplication of 11p15.5, pUPD of chromosome 11, rearrangement of maternal chromosome 11 involving the 11p15.5 region, or mutations

TABLE 11-7 Human UPDs Associated with a Growth or Endocrine Phenotype

Chromosome	Paternal/Maternal	Syndrome
6	p	Transient neonatal diabetes mellitus
7	m	Silver-Russell syndrome
11	p	Beckwith-Wiedemann syndrome
14	m	Hypotonia, motor delay, IUGR, and precocious puberty
15	p	Prader-Willi syndrome
16	m	IUGR, often with confined placental trisomy

of *CDKN1C*, a maternally expressed gene that lies centromeric to *IGF2*. Interestingly, there are some quite strong phenotype-genotype correlations, with hemihypertrophy being mostly associated with UPD and exomphalos being more common in patients with mutations of *CDKNIC.*

In contrast, Silver-Russell syndrome (SRS) is a condition where IUGR and poor postnatal growth are associated with other dysmorphic features. There is a characteristic facies; limb, cranial, or truncal assymetry; a striking lack of subcutaneous fat, particularly in infancy; and some rather variable minor dysmorphic features.[22] It is usually sporadic, but a number of published pedigrees would support autosomal dominant or recessive inheritance in some families. Recent molecular genetic findings were the observations of mUPD of chromosome 7 in approximately 7% of cases.[23] A role for an imprinting error and not a recessive gene was demonstrated by detailed studies of the grandparental origin of a large number of chromosome 7 DNA markers.[24] Further evidence comes from reports of two SRS patients with duplications of 7p11.2-p13, which includes an imprinted region of chromosome 7.[25] While there have been a number of candidate genes for SRS, at present none of these has a clearly defined role.

CONCLUSION

Childhood growth is often involved in genetic diseases that do not primarily involve the growth process. Growth as a process is affected by myriad other physiological systems, so that a significant disorder in one process may have an impact on growth by quite indirect pathways. In this chapter, we tried to concentrate on those genetic disorders that have a fairly clear direct impact on growth.

Down syndrome is the least specific and may still eventually be seen to disrupt normal growth by very indirect pathways. In contrast, Turner syndrome and other *SHOX*-related disorders have clear links to the growth process by the localization of expression of the gene. Further, in the case of the *FGFR3* and *DTDST* families, direct experiments have begun to define exact mechanisms whereby growth is perturbed.

Genomic imprinting and UPD, which often exposes the involvement of imprinted genes, are still in a rapidly developing field, and much detail needs to be added. However, the connection between imprinting and growth cannot be denied on present evidence. In addition to the few human disorders described here, a number of other imprinted genes are now involved in the growth process, in experimental systems at least.

FURTHER READING

Preece MA, Moore GE. Genomic imprinting, uniparental disomy and fetal growth. Trends Endocrinol Metab. 2000;11:270–275. This is a review of genomic imprinting and related phenomena and their relevance to growth and development.

Strachan T, Read AP. Human Molecular Genetics, 2nd ed. Oxford: BIOS Scientific Publishers, 1999:576. This is a general textbook of classical and molecular genetics. It is a particularly readable and comprehensive volume concerning underlying biology and techniques.

Vajo Z, Francomano CA, Wilkin DJ. The molecular and genetic basis of fibroblast growth factor receptor 3 disorders: The achondroplasia family of skeletal dysplasias, Muenke craniosynostosis, and Crouzon syndrome with acanthosis nigricans. Endocr Rev. 2000;21(1):23–39. This is a comprehensive review of the relevance of *FGFR3* in normal development and in bone dysplasias.

REFERENCES

1. Patton MA. Genetics. In: Campbell AGM, McIntosh N (eds). Forfar and Arneil's Textbook of Pediatrics. Edinburgh: Churchill Livingstone, 1998:45–78.
2. Fuentes JJ, Pritchard MA, Planas AM, Bosch A, Ferrer I, Estivill X. A new human gene from the Down syndrome critical region encodes a proline-rich protein highly expressed in fetal brain and heart. Hum Mol Genet. 1995;4(10):1935–1944.
3. Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet. 1997;16(1):54–63.
4. Shears DJ, Vassal HJ, Goodman FR, Palmer RW, Reardon W, Superti Furga A, et al. Mutation and deletion of the pseudoautosomal gene SHOX cause Leri-Weill dyschondrosteosis. Nat Genet. 1998;19(1):70–73.
5. Vajo Z, Francomano CA, Wilkin DJ. The molecular and genetic basis of fibroblast growth factor receptor 3 disorders: The achondroplasia family of skeletal dysplasias, Muenke craniosynostosis, and Crouzon syndrome with acanthosis nigricans. Endocrinol Rev. 2000;21(1):23–39.
6. Oberklaid F, Danks DM, Jensen F, Stace I, Rosshandler S. Achondroplasia and hypochondroplasia. Comments on frequency, mutation rate, and radiological features in skull and spine. J Med Genet. 1979;16:140–146.
7. Beals RK. Hypochondroplasia. A report of five kindreds. J Bone Joint Surg [Amer]. 1969;51(4):728–736.

8. Wilkin DJ, Szabo JK, Cameron R, Henderson S, Bellus GA, Mack ML, et al. Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. Amer J Hum Genet. 1998;63(3):711–716.
9. Bellus GA, McIntosh I, Smith EA, Aylsworth AS, Kaitila I, Horton WA, et al. A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet. 1995;10(3):357–359.
10. Horton WA, Rimoin DL, Lachman RS, Skovby F, Hollister DW, Spranger J, et al. The phenotypic variability of diastrophic dysplasia. J Pediatr. 1978;93(4):609–613.
11. Makitie O, Kaitila I. Growth in diastrophic dysplasia. J Pediatr. 1997;130(4):641–646.
12. Hastbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP, Daly M, et al. The diastrophic dysplasia gene encodes a novel sulfate transporter: Positional cloning by fine-structure linkage disequilibrium mapping. Cell. 1994;78(6):1073–1087.
13. Hastbacka J, Kerrebrock A, Mokkala K, Clines G, Lovett M, Kaitila I, et al. Identification of the Finnish founder mutation for diastrophic dysplasia (DTD). Euro J Hum Genet. 1999;7(6):664–670.
14. McGrath J, Solter D. Nuclear transplantation in the mouse embryo by microsurgery and cell fusion. Science. 1983;220:1300–1302.
15. McGrath J, Solter D. Development of mouse embryogenesis requires both the maternal and paternal genomes. Cell. 1984;37:179–183.
16. Surani MA, Barton SC, Norris ML. Development of reconstituted mouse eggs suggests imprinting of the genome during gametogenesis. Nature. 1984;308(5959):548–550.
17. Lawler SD. Genetic studies on hydatidiform moles. Adv Exp Med Biol. 1984;176:147–161.
18. McFadden DE, Kalousek DK. Two different phenotypes of fetuses with chromosomal triploidy: Correlation with parental origin of the extra haploid set. Amer J Med Genet. 1991;38(4):535–538.
19. Engel E, DeLozier Blanchet CD. Uniparental disomy, isodisomy, and imprinting: Probable effects in man and strategies for their detection. Amer J Med Genet. 1991;40:432–439.
20. Wramsby H, Fredga K, Leidholm P. Chromosomal analysis of human oocytes recovered from preovulatory follicles in stimulated cycles. N Engl J Med. 1987;316:121–124.
21. Malcolm S, Clayton-Smith J, Nichols M, Robb S, Webb T, Armour JAL, et al. Uniparental disomy in Angelman's syndrome. Lancet. 1991;337:694–697.
22. Wollmann HA, Kirchner T, Enders H, Preece MA, Ranke MB. Growth and symptoms in Silver-Russell syndrome: Review on the basis of 386 patients. Euro J Pediatr. 1995;154:958–968.
23. Kotzot D, Schmitt S, Bernasconi F, Robinson WP, Lurie IW, Ilyina H, et al. Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. Hum Mol Genet. 1995; 4(4):583–587.
24. Preece MA, Price SM, Davies V, Clough L, Stanier P, Trembath RC, et al. Maternal uniparental disomy 7 in the Silver-Russell syndrome. J Med Genet. 1997;34(1):6–9.
25. Monk D, Wakeling EL, Proud V, Hitchins MP, Abu-Amero SN, Stanier P, et al. Duplication of 7p11.2-p13, including *GRB10*, in Silver-Russell syndrome. Amer J Hum Genet. 2000;66:36–46.

12

SALTATION AND STASIS

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SALTATION AND STASIS: HOW CHILDREN GROW

How, exactly, does the single cell conceptus become a small but perfectly formed human being of some 35 cm by 25 weeks of gestation? And by what process does the average 50 cm newborn grow to become, on average, a some 5–6 foot adult individual? How is this much flexibility in outcome possible from the same system? The nature of the process by which individual human growth proceeds has yet to be clearly elucidated. Our understanding of the precise mechanisms or the cascade of events by which this increase in size unfolds remains a fuzzy outline at the present time. This is one of the most exciting questions in human biology. It is also one of the most troublesome in terms of our lack of knowledge. There is a pressing need to clarify the process of normal human growth: How should we proceed to treat short stature with growth hormone? How can we best use body size as a marker for intervention efforts in international health? Could we be better informed in our attempts to help premature infants develop normally?

During the past 20 years, data have been collected that identify the process of human growth as *saltatory*. Increase in the size of the body (e.g., length or height) is achieved through unique time-constrained growth episodes that occur only intermittently. Following the vocabulary for similar biological processes previously identified in neural tissue, we have called this growth pattern *saltatory* and the unique growth accretions, *saltations*.[1] These saltations of growth occur as increments of variable amounts within and between individuals, and the amount of growth per saltation varies by anatomical site (the legs grow more than the head at each growth episode).

These saltations were identified in humans when the total body length of infants was measured daily. At observations within this time frame, careful measurement techniques identify unique growth increment events that stand out by contrast with surrounding time intervals when no growth, or increase in size, occurs. These intervening time durations of no measurable accretion, or *stasis* in terms of incremental growth, separate the individual growth saltation events. Thus, growth in size can be visualized as a stepwise function, with pulsatile increases in size resulting in unique steps of variable heights (Figure 12-1).

For example, in infancy, total body length or height increments range from 4 to 20 mm during 24 hours, while head circumference saltations are about 2 to 3 mm in 24 hours. This is not an everyday event: In our data, saltations are separated in time by intervals ranging from 1 to more than 60 days when no measurable growth occurs. This time interval of no measurable increment varies both within individuals and between individuals. Developmental age is important: Individual children have more frequent saltations when they are infants than during midchildhood (unpublished data).

The present data outline that, at the level of the whole body, growth is a saltatory process, occurring by episodic saltations according to a temporal clock whose parameters have yet to be clarified. To date, it appears that growth saltations occur

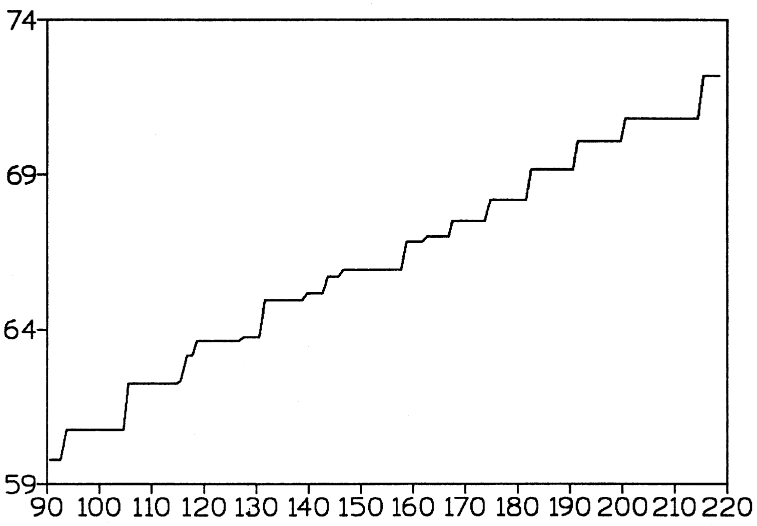


FIGURE 12-1 The saltation and stasis growth pattern from daily data (day of age, *x*-axis) of total body length measurements (cm, *y*-axis). The subject was a male infant followed from 90 to 218 days of age. These data were obtained after parental informed consent under a University of Pennsylvania–approved human subject protocol. Twelve statistically significant growth saltations contribute to the total growth during the interval. These occur at days 93 (0.98 cm), 105 (1.47 cm), 116 (0.81 cm), 118 (0.46 cm), 131 (1.2 cm), 143 (0.55 cm), 158 (0.92 cm), 167 (0.5 cm), 174 (0.68 cm), 191 (0.91 cm), 200 (0.72 cm), 215 (1.39 cm). Therefore, total growth was accrued on 12 days when variable amplitude growth saltation occurred after intervening stasis intervals of 2–16 days.

at aperiodic (noncyclical, or unequal) but nonrandom time intervals, observations that suggest the growth process is an expression of a nonlinear dynamical program.[2,3] This provides the ultimate flexibility for a biological system: It is likely that the variability in saltation amplitude and frequency is the mechanism that underlies the observable differences in size among individuals. The specific paths by which children achieve the same height are characterized by different series of unique increments in terms of the amount of growth per saltation and the total number of growth saltation events. Further, it is likely that height differences in adulthood are the result of the accumulation of different numbers of saltation events and the amount of growth at these saltations. It is hypothesized that saltatory growth is the mechanism by which variability throughout development is achieved and is the pathway by which genetics and environment orchestrate the unique growth patterns of individual children.

GENERATION OF THE SALTATION AND STASIS HYPOTHESIS

It is said that, often in the history of science, everyday observations lead to common knowledge about events that precede scientific discovery of these same occurrences by many years. How children grow is an excellent example of this dictum. The parents of the children who I observe often tell me that their grandmothers know perfectly well that children grow in spurts, and they ask me why we scientists need to study something so obvious.

Many different disciplines focus on issues in the study of human growth and development. Clinicians focus on identifying and treating the abnormally growing child. Cell biologists study the basic mechanisms by which cells divide and differentiate, thus contributing in their summation to growth increments. In the science of auxology and human biology, the greater part of the history of the science is characterized by the collection of data from worldwide populations. These studies measured children at relatively infrequent intervals, most often in annual and semiannual time frames. These data provided the basis for the commonly used growth reference charts, representing percentile distributions of height by age. These charts were intended to provide clinicians and public health professionals with a reference by which to assess normality of individual's progression through growth. The charts were constructed by applying a best-fitting curvilinear function to a set of sequential annual or biannual measurements, and these graphic representations became accepted as good approximations of the growth process during the time between data collection. According to the constructed charts, growth appears as a smooth and continuous daily accretion. This was assumed to be an accurate representation of the biology of growth. The error in this assumption is now clear. More frequently collected data elucidate the nature of the missing data and, thus, the growth process between annual data points. The more frequently collected data do not illustrate a linear and continuous daily accretion in size.

Instead, they document that growth occurs by a nonlinear and discontinuous, saltatory process.

METHODS: HOW THE GROWTH PROCESS IS IDENTIFIED

When the scientific question is the process and pattern by which individual children grow, the primary issues that must be considered include measurement protocol, assessment of measurement error, and the methods employed for data analysis.

Measurement Protocol

To begin to understand the underlying biological mechanisms that drive the growth process, it is necessary to conduct a time-intensive longitudinal study, following the growing organism at high frequency intervals. The phrase *short-term growth* has been coined to refer to such studies. While emphasizing the historically unique focus on growth over less than biannual intervals, the concept of "short-term growth" asserts that the goal of the study is to document growth during short intervals and presupposes that growth is always occurring, waiting to be documented. We prefer to think of investigations aimed at careful descriptions of individual patterns of the growth process as those involving time-intensive protocols, or time-intensive growth studies.

A serious consideration in designing a study aimed at elucidating the growth process is the sampling protocol. A measurement frequency must be chosen that provides adequate data in relation to the timing of the underlying growth events.[4] This is not always known in advance. Therefore, pilot studies are useful and often essential: The investigator chooses an initial window for sampling and changes the time frame as appropriate.

As an illustration, Figure 12-2 presents infant growth data as it would look if collected at monthly, biweekly, weekly, and daily intervals. These different amounts of information lead to quite different descriptions of the underlying growth process in this individual. The problem presented to the researcher who has collected such data and wishes to describe the growth pattern is this: how to identify what is happening between data points. If one has only data collected monthly, it is impossible to know the growth pattern over the course of the month. One can guess, and that is what researchers frequently do. In this example, for Figure 12-2A, it appears that a relatively continuous line might be a reasonable approximation of the path taken by the biological process between data points. Therefore, we might be tempted to connect the points and be satisfied that we understand, approximately, how this individual grew during this time interval. However, drawing a connecting line symbolically states that growth occurs every day between the points, at a relatively constant rate each day. This is an approach often employed in growth studies. Once such lines are drawn, they are used for deriving daily growth rates from the slope of the equation for the line.

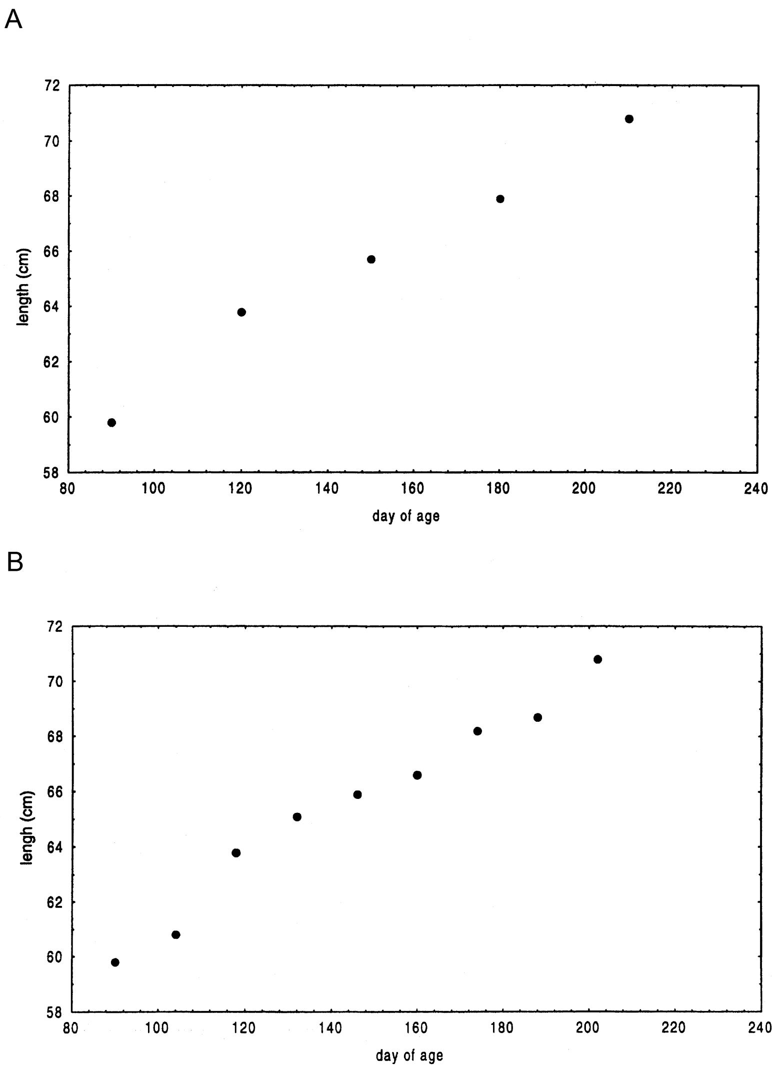
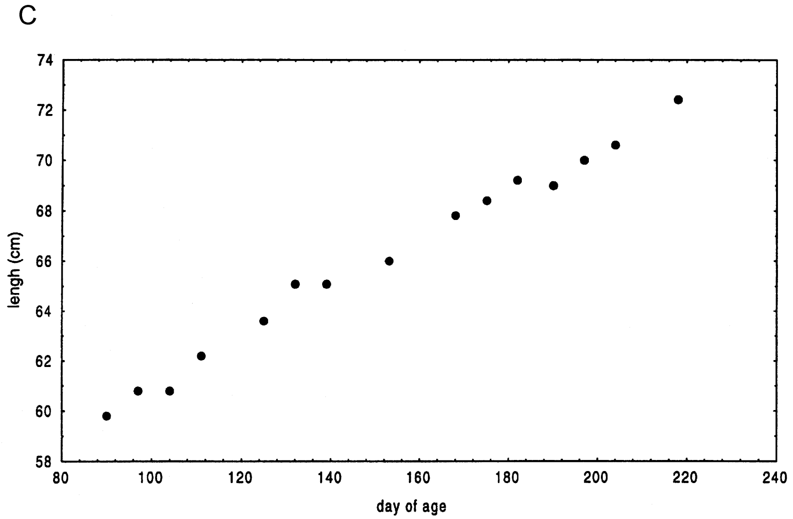


FIGURE 12-2 The effect of measurement interval on growth pattern identification. The experimental data from the infant described in Figure 12-1 are represented in four time frames: (A) data at 30-day intervals, beginning on study day 1; (B) data at 14-day intervals, beginning on study day 1; (C) data at 7-day intervals, beginning on study day 1; and (D) a subset of daily data from study day 1 to 73, for clarification of the growth pattern lost by less frequent measurements.

As more data are collected, as per our example in Figure 12-2, it becomes clear that this linear proposition might not be the actual or best description of how this individual is actually growing in length throughout the study interval. With data



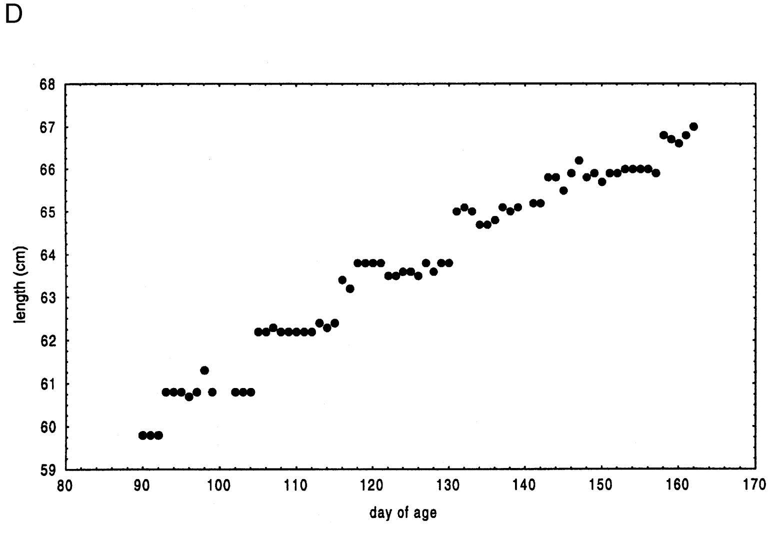


FIGURE 12-2 *(continued)*

collected at 2-week intervals (Figure 12-2B), the data suggest a nonlinear, perhaps continuous, growth pattern of variable growth rates. Weekly data (Figure 12-2C) suggest that a stepwise pattern might be the growth trajectory, and this impression is clarified by data collected daily (Figure 12-2D).

What is clear is that, with less frequent data, one cannot accurately identify the process between two data points. This example illustrates that growth data analysis problems are similar to the challenge of a connect-the-dots diagram in which the precise path becomes clarified only with increasing dots. The issue for the researcher interested in identifying the growth process is to collect sufficient information with which to reconstruct the biological process by which increase in size actually occurs.

Measurement Error Considerations

A second problem confronts the researcher when making a decision regarding measurement frequency: No measurement is free of error and certainly no human growth measurements are exempt from this consideration.[5] The sources of error at each measurement point reflect the precision of the instrument to accurately measure an object, the manner in which the object is measured, and any endogenous physiology that might contribute to variability in actual size. Therefore, consideration must be given to the technology employed, the researcher's ability to take the measurement, and the state of the subject.

To clarify the time window of observation for a study, it is necessary to conduct a pilot study to identify the actual measurement error of the particular observer and the subjects to be studied and to compare this measurement error with the incremental process under study. If biological increment and measurement error are equal, it would not be possible to identify changes in the data series due to biology from error. This is an often unappreciated reality of time-intensive investigations.

Moreover, the longitudinal nature of a time-intensive growth study magnifies these issues. Because the goal of investigation involves the pattern between data points, there is a critical need to pay attention to the effects that an error at one time has on the immediately adjacent points. Formally, this is known as an issue inherent to dependent, negatively correlated data.[6] An example of the magnitude of this problem would be the following: Imagine we have taken a measurement such that we have erred and now have a "too long" measurement at one time point. Through different errors, the first measurement is followed by a "too short" measurement at the subsequent data point. In our analysis, it might appear that no growth occurred between the two measurements as an artifact of the combined errors. Serial time-intensive data must always be analyzed by a statistical method that takes this possibility into its error assessment consideration.

In our saltatory growth studies, pilot studies are always undertaken to ascertain the measurement error levels with the instrument and sample to be studied. It is best if an independent study of replicate measurement reliability for all parameters to be measured is conducted and independent intra- and interrater measurement error ranges established. A pilot study of time-intensive serial measurements is also conducted. In the initial saltatory studies, the observation window of daily assessment was chosen after it was ascertained that technical errors of measurement were exceeded by measurement increments at the 95% confidence interval. Subsequently, careful documentation of intra- and interrater reliability was established in the actual longitudinal studies.

Data Analysis

A time-intensive longitudinal study produces a time series data set. However, the traditional time series methods presented in many popular statistical packages for the computer may not be the best approach to growth data analysis. Several issues intervene, the most significant of which is that many of these analytical methods are based on assumptions regarding patterns in the timing of events. These assumptions are likely not to be valid for biological data and may impose artifactual patterns, such as those resulting from Fourier time series analysis, to be discussed later.

A simple, direct method for time-intensive data analysis is to begin with an approach designed to ask, Where in a data series are significant differences between sequential measurements? With these identified, the sites of increments can be investigated for their own characteristics (duration and amplitude) and the intervals between these can be investigated for time duration, trends, and random error components. This approach makes no assumptions about the presence or characteristics of increments or the time between them. The critical aspect of time-intensive data analysis is the identification of actual growth increments from error components in the serial data. This is essential if the goal of the research is to describe the biological nature of the growth process or the time course and pattern of changes in size. If this step is omitted from an analysis, the results confound error and growth and may erroneously describe error components as biological growth pattern.

Each individual's growth trajectory is unique in terms of the timing and amount of growth at saltation events (Figure 12-3). In our studies, we analyze each individual's data separately because a group analysis would obscure saltatory growth as times of saltation and stasis would overlap between children (they do not occur with the same amplitude or timing). For an incremental analysis of individual data, the *t*-statistic for serially correlated data is applied to the sequential data.[7] This is an approach that has been used to identify significant differences in time series endocrinological data. This statistic identifies significant differences between sequential measurements only when those differences exceed an a priori level. We use a 95% confidence limit and the *t*-statistic cutoff point is calculated employing the individuals' pooled variance, reflecting the significant individual variability in measurement error and the sample size of measurements.[6] This approach accounts for the negatively dependent nature of serial data, makes no assumptions about the underlying temporal process of growth, and is relatively robust to nonnormal data. Thus, increments that are greater than this calculated value have a probability of about 1 in 20 that they represent random chance rather than significant change. The *t*-statistic for stricter levels of significance can also be employed, by altering the *t*-statistic value used.

This analysis permits the identification of statistically significant sequential positive and negative differences. Significant decreases that accompany significant increases are pairwise investigated for their correspondence to random error components and the remaining differences are further considered. This approach aims

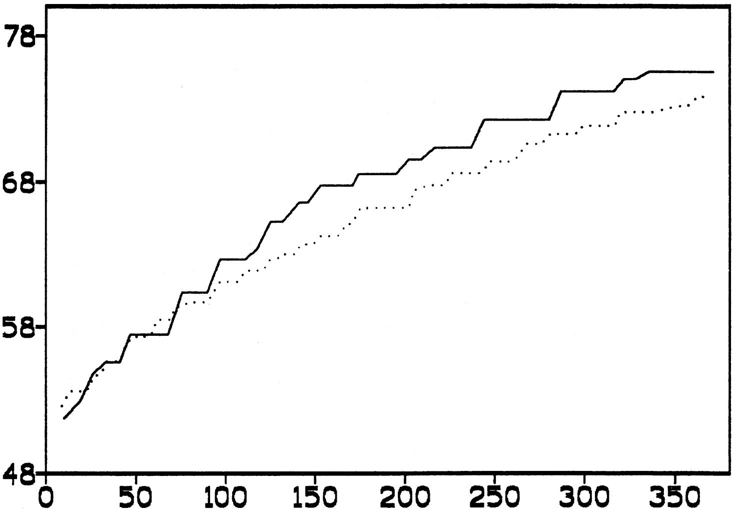


FIGURE 12-3 The saltation and stasis patterns for growth in length of two infants during their first year of life. Data were collected according to a University of Pennsylvania human subjects approved protocol.

to focus the analysis only on sequences in the data where the measurement method identifies significant change and aims to eliminate the description of error components as part of the biology of the growth process.

In our original infant length data analysis, growth increments were identified to punctuate serial measurements during which no significant changes were documented.[7] These observations led to the hypothesis that these intervals represented times during which either growth was unresolvable by measurement techniques or no incremental changes actually occurred. These alternatives were tested in this sample by a comparison of the total growth accrued by each individual during the study (size at the end of the study minus size at the beginning of the study) and the sum of the unique statistically significant growth increments found for each individual. If the stasis intervals were free of incremental growth, the two sums should be equal within measurement error, as the total growth of the child would be accounted for in the sum of the unique saltations. In this study, the total growth of the infants during their study was accounted for in the sum of discrete growth saltations. This analysis was the basis for the saltation and stasis hypothesis.

Therefore, one initial strategy in analyzing time-intensive measurements is to employ a method that asks, Can significant growth changes in the data be identified from measurement error? Methods for the analysis of saltatory growth must be based on discriminatory analytical methods that aim to identify significant change from error. It should be noted that data collection methods involving high error and children growing by low amplitude increments have a lower likelihood of saltatory growth resolvability.

The description of saltation and stasis just outlined is a hypothesis, or proposition, about the underlying biology responsible for growth, based on an incremental analysis of serial data and the resulting pattern of growth increments. The observation of such a growth pattern suggests that growth is a highly controlled event, not a continuous hourly and daily biological signal. The biological hypothesis is that growth is a two-phase process, consisting of a growth suppressive phase (stasis), putatively controlled by growth inhibitory proteins, and a discrete growth phase (saltations) that occurs episodically, due to either disinhibitory, permissive, or activation controls. This hypothesis is in line with what has been observed to characterize cell division and differentiation[8,9] and, thus, has strong support as a developmental process whose precise proximate controls remain to be elucidated.[10]

Mathematical Modeling

The incremental analysis led to the hypothesis that growth is a process of discrete increments separated in time by variable intervals of no growth. This observation is a statement that growth occurs by a process unfolding in time that can be visualized as a staircase, with different heights of stairs and different plateau lengths between the steps.

The proposal of a saltation and stasis pattern in the time series data can be statistically tested to see how well this hypothesis actually describes the data. This analysis requires a mathematical statement of the proposition that a stepwise mathematical function that is flexible in the amplitude and duration of the steps would be a good approximation of such a biological process and could provide an estimate of how well the hypothesis actually describes the time series data. The saltation and stasis mathematical model was developed by Michael Johnson, a biomathematician who had been working on similar problems in other biological systems.[11,12] The saltation and stasis mathematical model employs a pulse identification approach that is assumption free about how much growth occurs at a saltation and the timing between saltations. It explicitly tests the hypothesis of no growth between the events and identifies significant growth from error at a significance level set by the observer, using the entire raw data set and an error of measurement input by the observer.

Why use a mathematical model? Why not stop the data analysis after the incremental analysis and conclude that saltation and stasis was established? Mathematical models provide a statistically based description of how well a temporal pattern fits an entire data set and permits statistically based comparisons among competing patterns. Thus, the researcher can ask, Does a saltation and stasis pattern really describe the data better than a model of continuous daily growth? Or, is the saltatory growth notion some sort of artifact from errors in an incremental analysis? Alternatively, are there really stasis intervals between discrete growth changes, or do the growth events take longer than 24 hours, with some small growth continuing between each event? These questions are statements about entirely different views of the biological process of growth. The viewpoints can be directly compared as to which one best describes the serial growth data of individuals. The comparative approach is to apply a mathematical function that represents each of these conceptual patterns to the raw data. The "best fit" of the patterns is identified by a comparison of the statistical properties of the residuals, or differences between the fitted function and the experimental data points.

For example, in the infant length data, option 1 can be tested by fitting a simple curvilinear function through all of the data points, testing the hypothesis that growth is a continuous daily process. The application of such a function to the raw data in Figure 12-1 results in a number of data points that are not on the line (Figure 12-4). The residuals from these data points occur in a nonrandom, wavelike pattern about the line. This illustrates that the line representing the concept of continuous daily growth is not capturing a pattern that exists in the experimental data. The pattern of the residuals suggests that a stepwise or wavelike function is being overlooked by this application.

The second proposition, that growth is continuous but characterized by growth spurts that take more than 1 day to complete, is tested by fitting polynomial functions to the serial experimental data. The residuals of this application are likewise investigated for their pattern and magnitude. If a model fits a data set well, the residuals should be randomly distributed about the resulting model, as expected for random error, and the best-fitting pattern results in the smallest nonrandom error in the residuals. The stepwise saltation and stasis mathematical model (Figure 12-5) better fits the experimental data than a polynomial model (p <0.001).[3,12]

In this example, the saltation and stasis model is compared with two alternative patterns in terms of the magnitude and pattern of residuals. The saltation and stasis model is characterized by smaller, random residuals than either of these

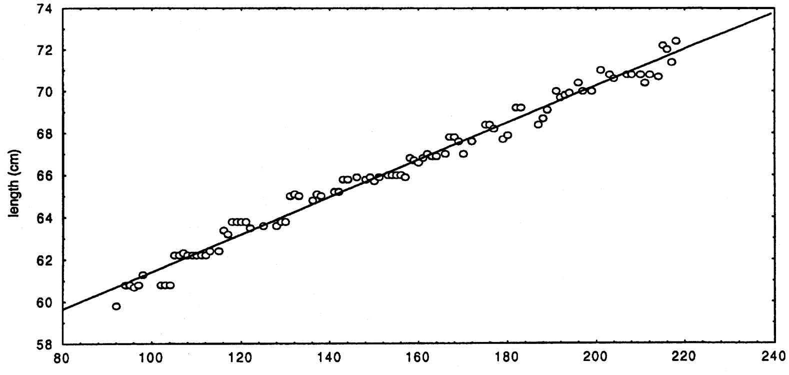


FIGURE 12-4 The data set for the infant in Figure 12-1 with a best-fit linear approximation. Note the pattern of data on either side of the line, a nonrandom residual pattern.

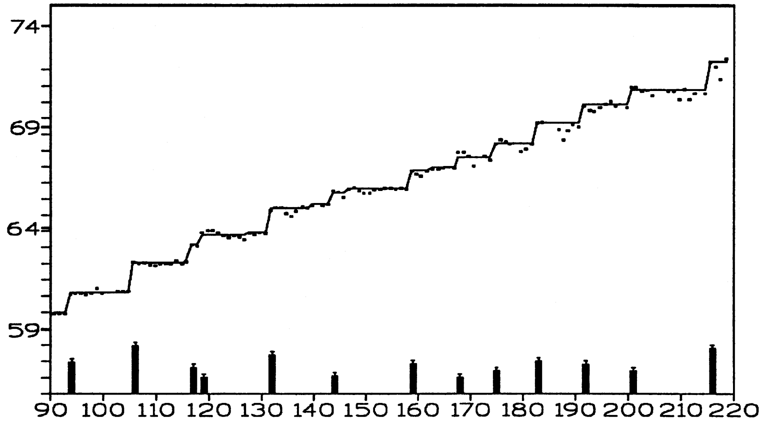


FIGURE 12-5 The saltation and stasis mathematical model fit to the data from the infant in Figure 12-1 with the statistically significant saltations shown below.

alternatives. This type of analysis does not exclude the possibility that other, untested models might not be equally good descriptions of the pattern of growth in these data. The analysis does identify that saltation and stasis better describes the data than models of continuous daily growth or a pattern of small and continuous mini growth spurts.

Therefore, mathematical models are useful for investigating propositions regarding the patterns in human growth data. They are particularly useful for comparing alternative hypotheses about the nature of the process and helpful for hypothesis generation regarding underlying mechanisms.

To the extent that a mathematical model is a good description of the data, the raw data fit the pattern closely. Raw data that do not fit into the pattern captured by an equation are the residuals. The better the model as a description of the data, the smaller are the residuals. A well-fit model has few residuals, and those represent random error. By fitting a variety of mathematical models to a serial data set, the researcher can objectively test alternative biological models of underlying mechanism.

A number of non-hypothesis-driven methods have also been applied to the same data to investigate alternative approaches for the identification of saltatory growth. Details of the methodological considerations established in these studies can be found elsewhere.[12–14]

One important research question involves identifying the nature of the temporal characteristics of saltatory growth.[2] Investigations completed thus far have asked two basic questions: Are growth pulses predictable, or are they entirely random? The question of whether growth saltations occur at consistent and regular stasis intervals was addressed employing Fourier time series analysis. This approach assumes that underlying mechanisms oscillate at a constant frequency, and it identified that saltations are nonperiodic in occurrence.

To investigate whether, by contrast, saltations occur randomly, two methods were employed. First, the observed stasis interval durations were compared to the binomial approximation for random intervals and the experimental intervals were found to be nonrandom. Second, Monte Carlo simulations of 1000 randomly spaced saltation events were compared with the observed stasis interval distributions in the data. The experimental stasis interval durations were identified as nonrandom.

These analyses led to the question, If a biological system is neither predictable nor random, what sort of system is it? We presently believe that growth proceeds according to nonlinear dynamical principles and is episodically irregular.[3] Such systems are typically found in complex, multinodally controlled networks,[15] which is the most likely description of the process of growth.[2]

Therefore, methods for the identification of saltatory growth must aim to identify any saltations present without imposing assumptions about the nature of the time between events and without creating artifactual temporal patterns in the data. Fourier time series analyses are an example of the first type of problem: These methods are a poor approach to data analysis because they assume that the data series under study exhibits periodic signaling. The method imposes this conformation on the data, whether or not it is extant in the original data series.[12,16] Many complex irregular temporal patterns are resolved by such a program to be periodic as the method attempts to characterize the unknown serial configurations as cyclical waves. The output of such an analysis does not necessarily accurately characterize the original data set. The researcher is left to compare the Fourier analysis results with those of other analytic methods to decide if the periodicities identified are meaningful.

In the second category are smoothing methods and moving average techniques. These approaches alter the temporal characteristics of the original data series and are inappropriate approaches for the identification of saltation and stasis because of the patterns that they induce.[29] These methods are particularly inappropriate for data series characterized by time-intensive changes, because they attenuate, or filter, high-frequency information. This method involves altering the original data series prior to analysis. The raw data are subjected to a moving average replacement regime: A select number of sequential measurements are averaged and this mean becomes the data point in the middle of this interval, replacing the actual measured values. This is repeated for the entire series, until a new time series data set is created that consists of a series of interval averages, moving through the data set (hence, the nomenclature *moving average approach*). In this way, a new data series is created that becomes the focus of analysis. Specifically, if a stepwise function is the actual pattern in the data, a moving average approach creates a slowly changing function and obscures the pattern of both saltation and stasis. Any characteristics of serial data analyzed by this method are subject to artifactual time characteristics of short-term changes and their characteristics.

From this overview, it can be summarized that, in the analysis of time-intensive data, it is insufficient to merely connect all raw data points and assume that the resulting pattern is meaningful: This would result in the identification of a pattern that confounds error with biological signal. While often used to correct for errors of measurement, moving averages are a faulty approach in saltatory growth analyses and further exacerbate the error and biological signal distinctions. It is optimal to employ a method that analyzes all the original raw measurement data without imparting any alterations or temporal characteristics. Finally, the identification of growth patterns should be amenable to statistical investigation and permit comparisons among models.

BIOLOGY OF SALTATORY GROWTH: MECHANISMS AND HYPOTHESIS TESTING

As parents of young children observe, children grow by leaps and bounds, intermittently. While the amount of growth per saltation varies and the exact time to expect a growth saltation cannot yet be identified, each growth episode is an experienced event for the individual child. Growth saltations are accompanied by changes in behavior: agitation, sleep and appetite increase, and illness episodes co-occur with growth saltations more than can be explained by chance alone.[17,18] These observations suggest that the process of growth, which we have for many years considered to be a process restricted to increase in size, may in fact reflect much more in terms of the maturation of the organism. Thus, growth *is* maturation and saltatory growth is the manifestation of this developmental program.

In support of this proposition, variability in patterns of growth saltation amplitude and timing reflect developmental age such that infants and adolescents have more frequent growth saltations than occur in childhood, a finding that may explain the variable growth rates with age documented in the velocity curves of human growth. The data that have been considered up to this point are measurements of total body length, height, and head circumference. What is happening at the level of individual body parts and how these are coordinated into whole-organism growth remains to be elucidated by future investigation.

Once generated, scientific hypotheses must be tested on novel data collected for that purpose. The experience garnered from the preceding studies emphasizes the importance of measurement technique and analytic strategies that are necessary to identify saltatory growth if it is present in data.

The saltation and stasis hypothesis was generated on longitudinal data of infant recumbent length. The proposition must be tested on original data collected to further investigate the growth process and underlying biological mechanisms that are presently unknown. The protocol of daily measurements has been applied to height during childhood and adolescence with similar results. Fetal ultrasound measurements have been taken at twice weekly intervals that clearly document intervals of stasis in fetal body parameters.[19] Daily measurements on the lower leg of human infants and children, collected by knemometric methods, have come to conflictual conclusions. While these data were analyzed by approaches that were not designed to identify saltatory growth, inspection of published graphs and the authors' conclusions that the data series contain both stasis intervals and times of growth that exceed measurement error[20,21] suggest that a saltatory process underlies the growth patterns in these data.

Animal studies are also providing interesting results. Daily measurements on rabbit tibia illustrate a pattern of growth that is linear, much like the results of monthly human measurements.[22] Rabbits measured at 3-hour intervals,[20] by contrast, show patterns of growth that are compatible with saltatory growth: intervals of growth and intervals of no growth.[10] What is clear from the animal studies is that growth is an expression of a species-specific development program. Time-intensive studies of rats and rabbits illustrate that the stasis interval duration and saltation frequency reflect the overall maturation of the organism. What is identifiable in a daily time frame for humans occurs within hours in these smaller animals, whose developmental rates are some 100-fold faster than humans. Therefore, the concept of "daily growth" is not a useful unit of investigation in future saltatory growth studies. What is remarkable in these investigations of animal growth patterns is how informative they are about the nature of growth as a part of the maturational program. It is likely that saltatory growth is a reflection of the aging process. While sensible from a lifetime perspective, it is rare that growth and aging are united in a research program.

The mechanisms that control the whole body growth pattern are as yet unknown. Biochemical and hormonal studies employing noninvasive investigative techniques in humans, such as urinary assays, are being initiated and suggest that this may an important avenue for future investigations. The first hormonal studies with the aim of further identifying within-day and between-day patterns of growth hormone and insulin growth factor secretion have been undertaken.[23] These questions were never previously investigated. Biochemical approaches for following bone growth in urinary excretions are being developed, too.[24]

Most recently, animal studies are beginning to investigate the patterns of change directly at the endochondral growth plate, the site of incremental growth of long bones (Wilsman and colleagues, unpublished data; see Wilsman et al.[25]). These studies aim to synthesize knowledge of cellular function and morphology with the actual mechanisms that may be responsible for incremental saltatory growth.

To understand the nature of the genetic, cellular, biochemical, and general hormonal mechanisms controlling the process of saltatory growth, innovative studies are needed. What seems clear is that there is a genetic basis to the timing of growth saltations: Identical twins are concordant in their timing (unpublished data) and population differences in saltatory growth pattern (the timing and amplitude of saltations) may be significant.[3]

Saltatory growth is hypothesized to reflect species-specific morphogenetic patterning: the pattern of growth events being a manifestation of protein action directed by genes controlling the development of species specific morphology and aging.

A reasonable hypothesis based on a synthesis of present scientific information is that the temporal aspects of the growth-maturation saltation episodes reflect an interaction between cell-intrinsic information (genes uniquely expressed in individual cell lines) and central neural signals mediated by endocrine, paracrine, and cytokine cascades.

For example, it is known that growth in the nervous system and bone occurs by cells that express genes according to a pattern determined by intrinsic programs and external cues.[26,27] Coordinated organismic growth, from a single cell to a three-dimensional form, reflects the expression of proteins transcribed according to a developmental timing intrinsic to cells of similar lineage, determined during embryogenesis, that is modifiable by external input during development.[28] From this viewpoint, external input includes the metabolic signals transmitted by substances such as growth hormone to locally active hormones and cytokines, more directly involved in cellular proliferation and differentiation. Saltatory growth emphasizes the importance of further investigations into the relationship between cellular division and protein synthesis in determining the increase in size and differentiation of the organism.

Knowledge of the specific mechanisms by which individual growth is controlled is an imperative for scientific research. Our ability to assist in the wide range of abnormal growth experienced by children is limited by the gaps in our understanding. The very basis of normal growth of the organism is at the interface not only of growth in the proportions and size of children but is the cornerstone in our understanding and, thus, ability to control abnormal growth in cancer. How growth is normally controlled is a basic question in biology and deserves intense investigation. If, in normal growth, as the saltatory proposition suggests, growth is a highly controlled and permitted event, occurring as a result of disinhibition, then the normal inhibitory control mechanisms should provide new insights into how to inhibit uncontrolled growth, employing normal cellular mechanisms.

For many years, investigations of how to assist poorly growing children at the population level have sought to understand how and when interventions may be most beneficial. It is likely that both growth faltering and catch-up growth may reflect the resetting of saltation pulse intervals by the complex network of controls that determine the process of growth, and there may be an optimal intervention strategy that can be identified.[2]

Certainly, a clear understanding of how children grow is important in understanding the process of development in general. Parents, confronted by the behavioral changes that accompany growth, may be better able to assist their children through these episodic events if they understand the nature of the events. Changes in appetite are central to difficulties experienced by breast-feeding women, who may benefit from understanding that growth may be a biological basis for some of the episodic crying spells of their young infants. Whether or not children experience growing pains during saltation events is not clear, but there is a high coincidence of painful limbs reported by children when they have been documented to be growing. Much work remains to be undertaken in the further elucidation of the normal process of human growth. Whether saltation and stasis will turn out to be the most accurate description of growth at the cellular, mechanistic level remains to be determined. It is a useful model with which to initiate study into the biology of individual growth and provides a strong theoretical framework with which to conceptualize growth from the level of the cell to the whole organism. The variability in saltation amplitude and frequency are mechanisms by which the tremendous variability in growth rate and size documented worldwide can be explained. As the process that takes one cell to a reproductive member of the species, growth must be a flexible system that responds to multiple inputs with robust adjustments. Saltatory growth permits multiple paths to final size, moderating maturation and size in a dynamic and interactive system.

REFERENCES

1. Lampl M, Veldhuis JD, Johnson ML. Saltation and stasis: A model of human growth. Science. 1992;158:801–803.
2. Lampl M, Johnson ML. Normal human growth as saltatory: Adaptation through irregularity. In: Newell K, Molenaar P (eds). Dynamical Systems in Development. Mahwah, NJ: Lawrence Erlbaum, 1998:15–38.
3. Lampl M, Ashizawa K, Kawabata M, Johnson ML. An example of variation and pattern in saltation and stasis growth dynamics. Ann Hum Biol. 1998;25:203–219.
4. Lampl M, Johnson ML. Identifying saltatory growth patterns in infancy: A comparison of results based on measurement protocol. Amer J Hum Biol. 1996;9:343–355.
5. Cameron N. The Measurement of Human Growth. London: Croom Helm, 1984.
6. Winer BJ. Statistical Principles in Experimental Design. New York: McGraw-Hill, 1971.
7. Lampl M. Evidence of saltatory growth in infancy. Amer J Hum Biol. 1993;5:641–652.
8. Edgar B. Diversification of cell cycle controls in developing embryos. Curr Opin Cell Biol. 1995;7:815–824.
9. Elledge, SJ. Cell cycle checkpoints: Preventing an identify crisis. Science. 1996;274:1664–1672.
10. Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999.
11. Johnson ML, Lampl M. Methods for the evaluation of saltatory growth in infants. Meth Neurosci. 1995;28:364–387.
12. Johnson ML. Methods for the analysis of saltation and stasis in human growth data. In: Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999:27–32.
13. Johnson ML, Veldhuis JD, Lampl M. Is growth saltatory? The usefulness and limitations of frequency distributions in analyzing pulsatile data. Endocrinol. 1996;137:5197–5204.
14. Schmid CH, Brown EN. A probability model for saltatory growth. In: Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999:121–131.
15. Pincus SM. Quantifying complexity and regularity of neurobiological systems. Meth Neurosciences. 1995;28:336–363.
16. Johnson ML, Lampl M. Artifacts of Fourier series analysis. Meth Enzymol. 1994;240:51–68.
17. Lampl M. Leaps and bounds: How children grow. Ped Basics. 1996;72:10–16.
18. Lampl M. Saltatory growth and illness patterns. Amer J Phys Anthropol. 1996;22(Suppl):45.
19. Bernstein IM, Badger GJ. The pattern of normal fetal growth. In: Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999:27–32.

20. Hermanussen M, Bugiel S, Aronson S, Moell C. A non-invasive technique for the accurate measurement of leg length in animals. Growth, Develop, Aging. 1992;56:129–140.
21. Hermanussen M, de los Angeles Rol de Lama M, Burmeister J, Fernandez-Tresguerres A. Microknemometry: An accurate technique of growth measurement in rats. Physiol Behav. 1995;2:347–352.
22. Oerter Klein K, Munson PJ, Bacher JD, Culter Jr GB, Baron J. Linear growth in the rabbit is continuous, not saltatory. Endocrinol. 1994;134:1317–1320.
23. Gill MS, Thalange NKS, Diggle PJ, Clayton PE. Rhythms in urinary growth hormone, insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 excretion in children of normal stature. In: Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999:59–70.
24. Branca F, Robins S. Saltatory growth: evidence from biochemical measurements. In: Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999:90–99.
25. Wilsman NJ, Farnum CE, Leiferman EM, Lampl M. Growth plate biology in the context of growth by saltations and stasis. In: Lampl M (ed). Saltation and Stasis in Human Growth and Development: Evidence, Methods and Theory. London: Smith-Gordon, 1999:71–87.
26. Poliard A, Ronziere MC, Freyria AM, Lamblin D, Herbage D, Kellermann O. Lineage-dependent collagen expression and assembly during osteogenic or chondrogenic differentiation of a mesoblastic cell line. Exp Cell Res. 1999;253(2):385–395.
27. Qian X, Goderie SK, Shen Q, Stern JH, Temple S. Intrinsic programs of patterned cell lineages in isolated vertebrate CNS ventricular zone cells. Develop. 1998;125:3143–3152.
28. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: Cell fate control and signal integration in development. Science. 1999;284:770–776.
29. Lampl M, Johnson ML. Wrinkles induced by the use of smoothing procedures applied to serial growth data. Ann Hum Biol. 1998;25:187–202.

13

BODY COMPOSITION DURING GROWTH AND DEVELOPMENT

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INTRODUCTION

Changes in the chemical composition of the body occur throughout the life cycle, influenced by growth, maturation, and aging as well as other factors, such as disease and behavior. The chemical composition represents the absolute amounts and relative proportions of lipid, protein, water, and minerals in the body. Changes in the chemical composition of the body are an integral part of the biological changes of the life cycle. This chapter reviews the conceptual models that form the basis of body composition studies, methods of assessing body composition, the changes in body composition associated with growth and maturation, the role of body composition in determining nutritional needs, and factors that influence body composition, such as diet, heredity, environment, behavior, and disease.

BASIC CONCEPTS

Chemical Maturation and the Life Cycle

From the moment of conception, the proliferation, differentiation, expansion, and replacement of cells is largely regulated by the DNA code in the cell nucleus. At the level of the organism, this process is viewed as growth and development, but at the microscopic level, the process results in changes in the relative and absolute amounts of chemical compounds in the body. For example, at birth, the brain and other organs form a very large proportion of both lean body mass and total body mass. As the infant grows, the skeletal muscle compartment expands. Although the brain and other organ tissues continue to grow, they gradually come to represent proportionately less of the lean and total body mass. Similarly, at birth, many bones are present as ossification centers and are gradually filled in with bone matrix of hydroxyapatite. During pregnancy, lactation, and senescence, bone mass fluctuates and declines. Thus, the calcium content of the body shifts as the body matures and ages. These examples illustrate the process of chemical maturation and how the composition of the body changes during the life cycle.

Body Composition Models

The composition of the body can be evaluated at numerous levels of biological complexity, from basic elements (e.g., carbon, oxygen, and hydrogen), molecules (water, lipids, protein), to whole tissue compartments (fat, muscle, and bone) of the human body as illustrated in Figure 13-1.[1] Each of these levels of biological complexity provides different kinds of information about how the body changes and matures during growth and development. Furthermore, these levels of com-

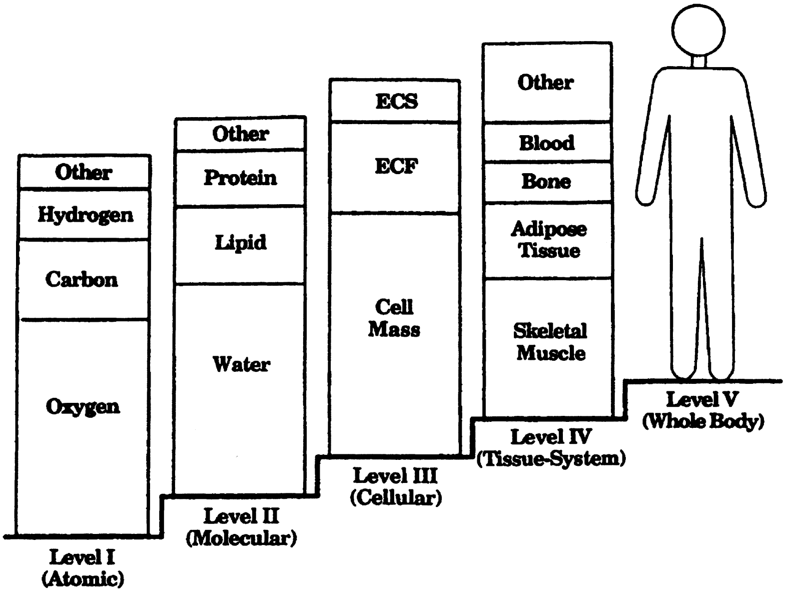

Other
Hydrogen
Carbon
Oxygen
Level I
(Atomic)
Other
Protein
Lipid
Water
Level II
(Molecular)
ECS
ECF
Cell
Mass
Level III
(Cellular)
Other
Blood
Bone
Adipose
Tissue
Skeletal
Muscle
Level IV
(Tissue-System)
Level V
(Whole Body)

FIGURE 13-1 The five-level model of human body composition. ECF and ECS are extracellular fluids and solids, respectively. (Source: Wang et al.[1])

plexity provide a framework for choosing the appropriate level of focus for the question at hand. For example, use of supplemental growth hormone in athletes resulted in increased fat-free mass (the muscle and bone compartment of the body) but not increased muscle strength.[2] The resulting increased fat-free mass may have an altered chemical composition due to an increase in the water or connective tissue component of fat-free mass. Thus, the framework helps delineate the relationships between changes at the tissue and cellular or molecular levels. In addition, this framework is useful in defining the limitations of current knowledge of body composition in the life cycle, since we are restricted by the ability to measure various compartments safely, accurately, and reliably in vivo. This is a special consideration in studies of infants and young children for whom certain methods, used in adults, are not feasible.

Many of the methods used to measure body composition are described in this chapter. The most commonly used methods partition the body compartments into two compartments (fat-free mass and fat mass), but some more recent methods use three compartments (lean, fat, and bone mass). Although the terms *fat-free mass* and *lean body mass* are often used interchangeably, fat-free mass consists of body weight minus the ether-extractable lipid fraction of the body (fat mass), whereas lean body mass also contains a small amount of essential lipid (2–3%). Bone mineral is part of the fat-free mass compartment. The newer techniques of bone densitometry (described later) allow for separate assessment of bone mineral mass from lean tissue and fat.

Nutrition, Adaptation, and Functional Outcomes

The chemical changes in the body during growth depend on the availability of a nutrient substrate, so nutrition can play a vital role in body composition. Essential nutrients in adequate quantities are required to assure that the cell growth, proliferation, and differentiation genetically programmed to occur can proceed unhindered. Furthermore, the relationship between body composition and nutrition is synergistic, in that nutrient requirements are determined, in part, by the composition of the body. For example, lean body mass (mainly the smooth and skeletal muscle compartments) is the most metabolically active part of the body and is the primary determinant of energy requirements in normal individuals. With a deficit in energy intake, both fat and lean body mass are used as fuel. The resulting weight loss is composed of loss in both these tissue compartments, and these changes alter the energy required for weight maintenance.

Body composition is also sensitive to behavioral patterns in a similarly synergistic manner. For example, physical activity promotes development and growth of the muscle and bones and prolonged inactivity results in muscle wasting and bone loss. Likewise, physical activity and endurance may be limited by inadequate muscle development. Thus, body composition both reflects and contributes to human adaptation to lifestyles, activity and work patterns, and the social and physical environment.

Tempo of Growth

As a child ages and sexual maturity approaches, the hormonal changes associated with puberty produce rapid changes in body composition. Body composition, especially in late childhood and adolescence, is regulated by a "biological clock" rather than chronological time. Children of similar age may be very different in terms of their physical maturation. Similarly, children of the same body size (stature or weight) may be of different ages or stages of maturation due to the biological clock or "tempo of growth." Variability in body composition, between and within populations, may be mediated by differences in the tempo of growth.

Fatness versus Fat Patterning

Adipose tissue is an important body component for survival. It serves as a reservoir for energy during periods of nutritional deprivation, and it insulates the body from the environment to maintain thermal homeostasis. Excess adipose tissue, or obesity, is associated with a cascade of physiologic abnormalities that can threaten health and well-being, as described later. A further consideration is the distribution of fat on the body, or fat patterning. A centralized fat distribution, one that has a greater proportion of fat on the trunk of the body compared to the extremities, is associated with metabolic abnormalities and therefore represents a risk of health complications independent of the actual amount of excess fat. Typically, fat patterns are characterized as "android," with a greater amount of fat on the trunk and less on the extremities, versus "gynoid" with greater amounts of fat on the hips and extremities than on the trunk of the body.

Heredity versus Environment

Body composition has a strong heritable component, although individual genes have not been identified. Measures of body size, such as height, weight, and body mass index have a strong genetic component. Familial aggregation studies also show significant heritability of fat, fat-free mass, and fat patterning.[3] There are also ethnic differences in fatness and fat patterning,[4,5] body density,[6] and bone mineral density. Despite these findings there is a large margin for environmental influences. The role of the environment in the development of excess adiposity is evidenced by the increasing rate of obesity in the United States[7] and some developing countries.[8] Studies of monozygotic and dizygotic twins have been useful in characterizing the gene-environment interactions; in particular, the similar responses of twins in studies of overfeeding and negative energy balance (weight loss) show a genetic basis to the way in which the body responds to changing environments.[3]

METHODS

The techniques used to assess body composition are an important part of the field itself, because of the shortcomings and limitations of all methods. With the exception of cadaveric studies, nearly all other body composition methods are indirect and involve assumptions that may introduce a bias in the results. Therefore, each method needs to be evaluated in the context of the quality of information obtained, the level of expense and risk involved, and the biological issue of interest for any given research study. Only through this informed approach have we attained an understanding of the changes in body composition through the life cycle.

Anthropometry

With measurements obtained by a well-trained anthropometrist, anthropometry under many circumstances can be a highly suitable method for body composition assessment, especially for population-based studies. The tools are moderately simple, precise, portable, and inexpensive; and the anthropometric exam is rapid and noninvasive. The tools used for anthropometric evaluations include scales, stadiometers, anthropometers, tape measures, and skinfold calipers. Weight and length or stature, the most basic information used to assess growth and nutritional status, are also used to form indices that provide an approximate representation of body composition. The most commonly used index is the body mass index (BMI), calculated as weight(kg)/stature(m)^2. BMI is useful as a screening tool for both excess adiposity and malnutrition, although it has several drawbacks; during adolescence, it is influenced by the timing of puberty and may poorly represent adiposity. In addition, a high BMI may be due to high lean body mass and normal adiposity. The U.S. Centers for Disease Control and Prevention recently recommended the use of BMI growth charts for screening overweight in children,[9] and international standards for BMI have also been developed.[10]

Upper arm anthropometry is also widely used as an indicator of the composition of the whole body. Mid-upper arm circumference and triceps skinfold thickness measures are used to compute the total area, fat area, muscle area, and muscle circumference of the upper arm (Table 13-1). At the population level, these measures correlate well with whole body measures of body fatness and muscularity even though they are measured at a single site. In addition, excellent reference data are available for these derived measures,[11] so that it is possible to assign a percentile rank or standard deviation score to an individual's measure, which indicates whether that person is relatively muscular or fat in comparison to same age-and-sex peers.

Anthropometric measures can also be used to estimate whole body fat-free mass, fat mass, and percent of body fat. This technique is based on prediction equations established from comparisons of skinfold measures with a criterion method such as hydrodensitometry (see later). These models assume that the prediction equations

TABLE 13-1 Formulas for Computation of Upper Arm Indicators of Body Composition

Upper arm muscle circumference (mm) = $C - \pi T$
Upper arm area (A) (mm^2) = $(\pi/4)\ (C/\pi)^2$
Upper arm muscle area (M) (mm^2) = $([C - \pi T]^2)/4\pi$
Upper arm fat area (F) (mm^2) = $A - M$
C = upper arm circumference; T = triceps skinfold

Note: Check the units, convert arm circumference to mm by multiplying by 10.

Source: From Frisancho.[11]

are generalizable from the samples from which they were derived and that body density is the same across varying age and sex groups. Despite these assumptions, the FFM and FM estimates correlate well with independently derived estimates such as DEXA.[12] Table 13-2 provides sets of prediction equations that illustrate age-, gender-, and ethnicity-specific equations. Anthropometric measures are also used to derive indicators of fat patterning, such as the waist-hip ratio (using waist and hip cir-

TABLE 13-2 Equations for Predicting Body Composition from Anthropometry

Two-skinfold method for prediction of percent body fat:[a]

Prepubescent white males:	% body fat = $1.21\ (T + S) - 0.008\ (T + S)^2 - 1.7$
Prepubescent black males:	% body fat = $1.21\ (T + S) - 0.008\ (T + S)^2 - 3.2$
Pubescent white males:	% body fat = $1.21\ (T + S) - 0.008\ (T + S)^2 - 3.4$
Pubescent black males:	% body fat = $1.21\ (T + S) - 0.008\ (T + S)^2 - 5.2$
Postpubescent white males:	% body fat = $1.21\ (T + S) - 0.008\ (T + S)^2 - 5.5$
Postpubescent black males:	% body fat = $1.21\ (T + S) - 0.008\ (T + S)^2 - 6.8$
All females:	% body fat = $1.33\ (T + S) - 0.013\ (T + S)^2 - 2.5$
When sum of triceps and subscapular skinfolds is greater than 35 mm, use	All males: $0.783\ (T + S) + 1.6$ All females: $0.546\ (T + S) + 9.7$

Four-skinfold method for prediction of percent body fat:[b]

Prepubertal children (1–11 years old)[14]
  Males: Density = 1.1690 – 0.0788 log sum of four skinfolds
  Females: Density = 1.2063 – 0.0999 log sum of four skinfolds
Adolescent children (12–16 years old)[15]
  Males: Density = 1.1533 – 0.0643 log sum of four skinfolds
  Females: Density = 1.1369 – 0.0598 log sum of four skinfolds
Percent body fat = (4.95/body density – 4.5) 100

[a] T = triceps and S = subscapular; from Slaughter et al.[13]

[b] Sum of four skinfolds = (triceps + biceps + subscapular + suprailiac); from Brook[14]; Durnin and Rahaman.[15]

Source: Adapted from Zemel et al.[16]

cumference) or the centripetal fat ratio defined as subscapular skinfold/(triceps + subscapular skinfold), using the triceps and subscapular skinfold measures.

Body breadth measures, such as biacromial, biiliac, elbow, and wrist diameters can be informative as part of the anthropometric description of body composition,[17] although they have not been used extensively. Because they quantify frame size, they correlate well with measures such as bone mineral density or can be used to distinguish between large- versus small-frame individuals when BMI is being used to characterize adiposity.

Densitometric Methods

Densitometric methods utilize the principle that body density can be determined as body mass divided by volume. Body density is then used to estimate fat-free mass, fat mass, and percent body fat, using conversion formulas. The method is based on several assumptions, including the assumption that the densities of the major tissue compartments (density of fat = 0.900 g/cc and fat-free mass = 1.100 g/cc) are relatively constant across individuals. However, these constants vary with growth and maturation, illness, extreme obesity, and aging. The Siri and Brozek formulas (Table 13-3) are the most widely used conversion formulas in adults. Lohman and colleagues revised the technique to account for differences in bone mineral content, since bone mineral content affects the density of fat-free mass (Table 13-3). In addition, Lohman[19] proposed an alternative set of age- and gender-specific constants for children, to be used in the prediction of body fat from an equation, due to the chemical immaturity of the growing child (Table 13-4). In children and adolescents, the chemical composition of the body changes, particularly with respect to the decreasing water and increasing mineral content of fat-free mass. For example, the density of fat-free mass in 8-year-old boys is 1.081 g/cc and for girls it is 1.079 g/cc, as opposed to the value for adults of 1.100 g/cc.

Hydrodensitometry, or underwater weighing, at one time was the most readily available criterion method for assessment of body composition (fat-free mass and fat mass). It has been used mainly in adults and adolescents and can be used in children (≥ 8 years) who are healthy, ambulatory, and have normal cognitive status. Body volume is determined from the measurement of body mass in air and while immersed in water using Archimedes' principle, according to which the apparent weight of an object immersed in water, relative to its weight in air, is

TABLE 13-3 Prediction of Body Fat Using Body Density Measurements

Siri (1956)	$\%\text{ body fat} = (4.95/D_b - 4.50) \times 100$
Brozek (1963)	$\%\text{ body fat} = (4.570/D_b - 4.142) \times 100$
Lohman (1986)	$\%\text{ body fat} = (6.386/D_b + 3.961m - 6.090) \times 100$

Note: D_b is the measured density of the body and m is the bone mineral.

Source: Adapted from Going.[18]

TABLE 13-4 Age and Gender Specific Constants for Prediction of Body Fat from Body Density

	Males		Females	
Age (yr)	C_1	C_2	C_1	C_2
1	5.75	5.36	5.69	5.33
1–2	5.64	5.26	5.65	5.26
3–4	5.53	5.14	5.58	5.20
5–6	5.43	5.03	5.53	5.14
7–8	5.38	4.97	5.43	5.03
9–10	5.30	4.89	5.35	4.95
11–12	5.23	4.81	5.25	4.84
13–14	5.07	4.64	5.12	4.69
15–16	5.03	4.59	5.07	4.64
young adult	4.95	4.50	5.05	4.62

Note: Where % body fat = $[C_1/D_b - C_2] \times 100$.

Source: From Lohman.[19]

decreased by an amount equal to the weight of the displaced water. One milliliter of water has a mass almost exactly equal to 1 gram. Therefore, the difference between the mass in air and the mass under water (in grams) is equivalent to the volume (in milliliters) of the object. The density is then calculated as mass divided by volume. Corrections are needed for the volume of air in the lungs and intestines and for the density of air and water.

Air displacement plethysmography is similar to hydrodensitometry in using mass and volume to measure body density. This method uses the displacement of air to estimate body volume. Figure 13-2 shows a Bod Pod® body composition analyzer, containing a two-compartment chamber of known size. Using a pulsating diaphragm between the two chambers to vary the pressure, the displacement of air when a subject is seated in the outer chamber is measured. A breathing apparatus is built into the device to estimate lung volume for a more accurate estimate of body density. Once body density is determined, the calculations are similar to those for hydrodensitometry.

A major source of bias in the densitometric methods involves assumptions about the water and mineral content of the fat-free mass. Multicompartment approaches that include other measures, such as total body water (TBW) to measure the water content of the fat-free mass or dual energy absorptiometry to measure the bone mineral content, greatly improve the accuracy of body composition estimates, especially in growing children.

Isotope Dilution Methods

Stable isotopes are used to estimate the size of various compartments of the body using the classic dilution principle. Provided proper sampling, dosing and

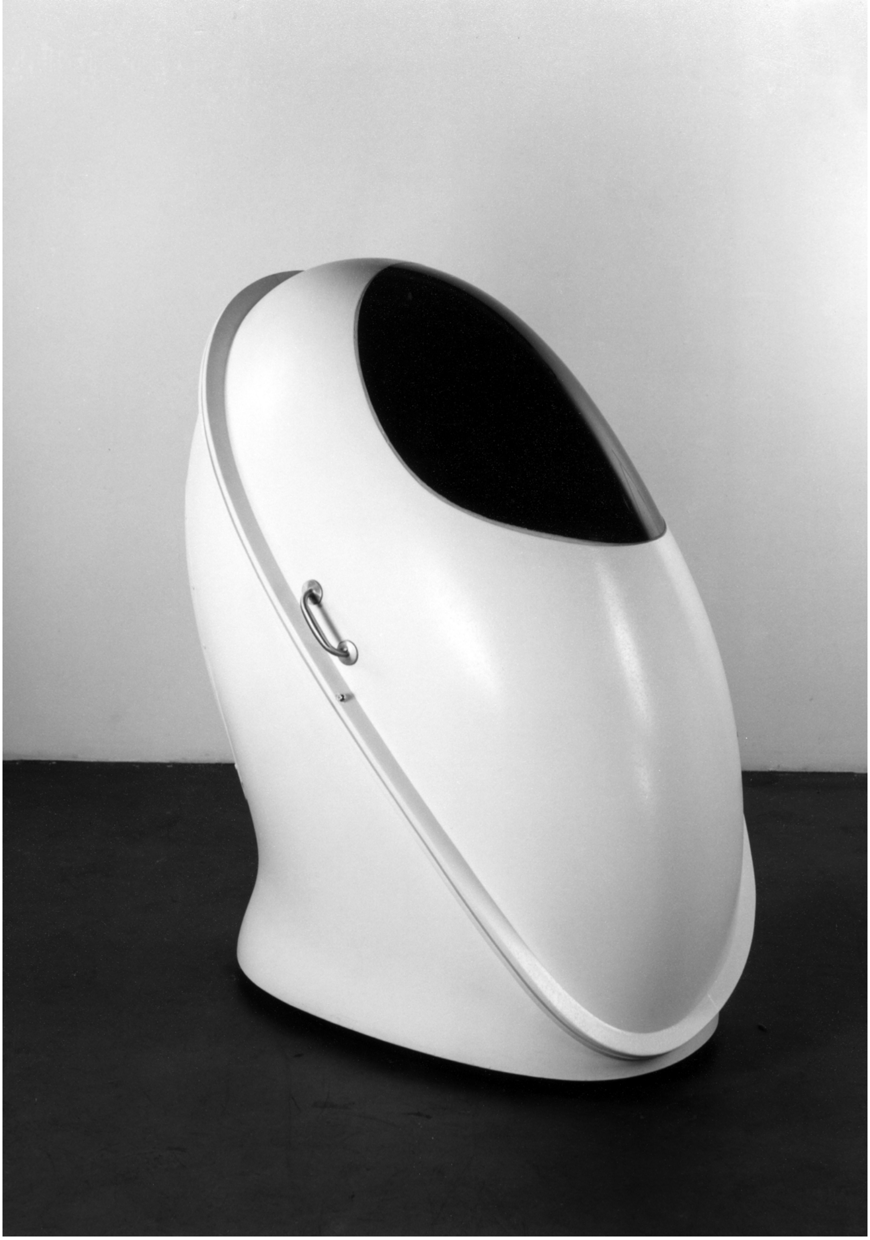


FIGURE 13-2 The Bod Pod® (Life Measurement Instruments, Concord, CA) is an air-displacement plethysmograph that measures fat-free mass and fat mass.

storage procedures are followed, this method is very accurate and measurement error is mainly related to the laboratory analysis of the isotopic concentrations. The stable isotopes, deuterium oxide (^2H_2O) or oxygen-18 (O^{18}), are naturally occurring isotopes. They are a safe, effective, and noninvasive means of measuring the size of the total body water pool in infants and children. Because they are naturally occurring isotopes, they are already present in the body and a baseline body fluid sample (such as urine) must be obtained. Then, a concentrated dose of isotope is administered orally that elevates the concentration of the isotopes in the body above that observed from drinking water. After an equilibration period, during which the isotope mixes with the total body water pool (usually about 4 hours), further sample collections are made for analysis by mass spectrometry. The rise in isotopic concentrations from baseline to the postdose equilibrium is proportional to the total amount of water in the body. Due to mixing of the isotopes with non-aqueous fractions of the body, ^2H_2O overestimates TBW by about 4%, and O^{18} overestimates TBW by about 1%. Fat-free mass is derived from the TBW measurement using hydration factors (Table 13-5) that estimate the fraction of the total body water in fat-free mass. Once fat-free mass is estimated, fat mass and percent of body fat can then be derived (Fat mass = Body weight – fat-free mass; Percent body fat = fat mass/body weight × 100).

As with the densitometric methods just described, isotope dilution methods are used to estimate fat-free mass and fat mass, and these estimations assume constant relationships that often fail to account for the chemical maturity of the subject or

TABLE 13-5 Hydration of the Fat-Free Mass in Children

	Females			Males		
Age	Wt (gm)	TBW (ml)	%FFM (gm)	Wt (gm)	TBW (ml)	%FFM (gm)
Birth	3325	2280	80.6	3545	2467	80.6
1 mo	4131	2716	80.1	4452	2966	80.1
2 mo	4989	3071	79.7	5509	3450	79.8
3 mo	5743	3407	79.5	6435	3848	79.6
6 mo	7250	4124	78.9	8030	4646	79.2
9 mo	8270	4777	78.6	9180	5392	78.9
1 yr	9180	5374	78.3	10,150	6050	78.6
2 yr	11,910	7215	77.7	12,590	7713	77.7
3 yr	14,100	8721	77.4	14,675	9134	77.0
4 yr	15,960	9995	77.3	16,690	10,534	76.6
5 yr	17,660	11,112	77.1	18,670	11,893	76.1
6 yr	19,520	12,301	77.0	20,690	13,300	75.8
7 yr	21,840	13,699	76.9	22,850	14,733	75.5
8 yr	24,840	15,436	76.8	25,300	16,215	75.2
9 yr	28,460	17,464	76.6	28,130	17,919	74.9
10 yr	32,550	19,656	76.5	31,440	19,843	74.6

Source: From Schoeller.[20]

other sources of biological variability. Isotope dilution methods assume a constant relationship between total body water and fat-free mass. This method has been greatly improved by recent studies that provide age-appropriate hydration factors for children (Table 13-5). Variability in bone mineralization can also contribute to sources of error in total body water derived estimates of body composition.

The compartmentalization of water in the body can also be determined using the isotope dilution method. Bromide and isotopic chloride dilution are used to estimate the extracellular water compartment so that the distribution of the total body water pool into the intra- and extracellular water compartments can be determined.

Bioelectrical Methods

Several body composition techniques have been developed based on the electrical properties of water and electrolytes in the body. Total body electrical conductivity (TOBEC) devices for infants and adults provide accurate, rapid, noninvasive estimates of fat-free mass, fat mass, and percent body fat. The TOBEC device consists of a low-energy electromagnetic coil through which the body passes on a gantry table. Disturbances in the measured conductance as the body traverses the coil, caused by the water and electrolytes in the body, are measured, and the signal is converted to body composition estimates by computerized prediction equations developed for this methodology. The adult device can be used with children as young as 4 years old; however, its accuracy in children under the age of 8 is uncertain. The infant TOBEC is suitable for children up to 1 year old.

Bioelectrical impedance analyzers (BIA) are another class of devices, using a slightly different technology, which measures the impedance of a low-energy electrical signal as it passes through the body. The body fluid compartment, rich in electrolytes, has the least impedance to the flow of an electrical signal, whereas the lipid and bone compartments have greater impedance. Older devices used source and detector electrodes placed on the hand and foot to measure impedance of the entire body, or at other locations to determine impedance of body segments. Newer BIA models are similar to bathroom scales, with metal foot pads for bare feet. In all models, there are assumptions about the shape and distribution of the tissues being measured and calibration equations are needed to convert the resistance signal to estimates of body composition. Care should be taken to use the prediction equations devised for children.

Potassium-40

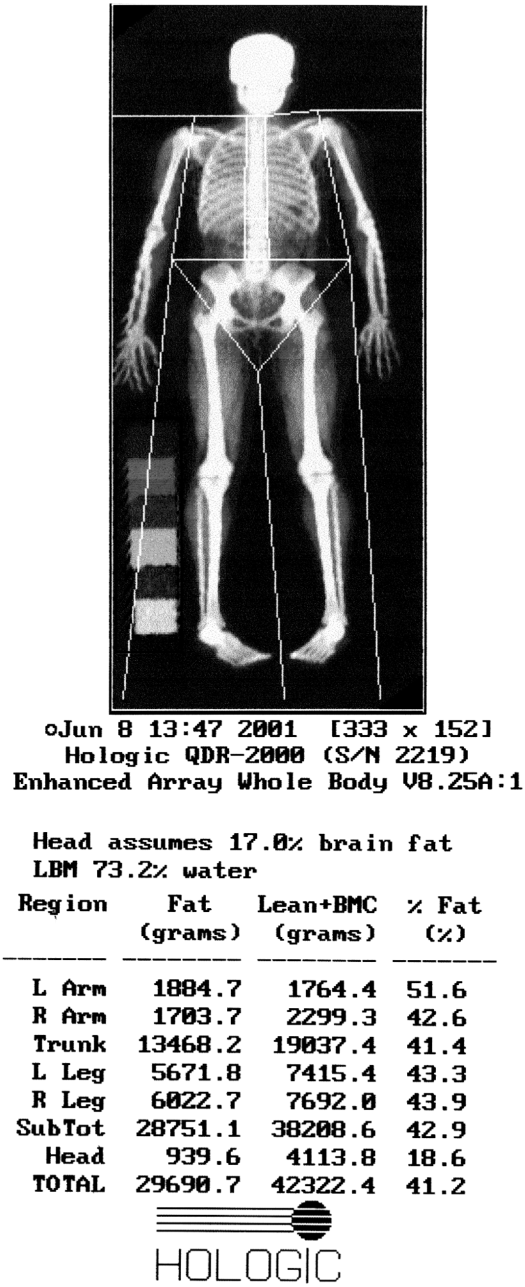
Potassium is found mostly in the intracellular fluid and can be used to estimate the body cell mass. The body cell mass is the fat-free intracellular space and the most metabolically active part of the body.[21] The body cell mass consists of the intracellular fluids and a smaller proportion of intracellular solids of the organs and muscles and excludes extracellular fluids and solids (such as bone mineral and collagen). A constant ratio of intracellular fluid to body cell mass is assumed, so measurement of total body potassium can be used to estimate body cell mass (body cell mass = total body K (mmol) × 0.0083). Potassium (^{40}K) is a naturally occurring stable isotope found in human tissue. It occurs as a very small percentage (0.0118%) of the non-radioactive ^{39}K also present in the body. ^{40}K emits a strong gamma ray that can be counted in a lead-shielded room (^{40}K counter) with a gamma ray detector for determination of the whole body content of ^{40}K. The total body potassium = ^{40}K/0.0118%. Since potassium is within the intracellular space, ^{40}K also can be used in combination with TBW to estimate the intracellular and extracellular fluid compartments of the body.

Absorptiometry Methods

The earlier absorptiometry methods used dual photon absorptiometry (DPA) using a radionuclide source and digital detector to determine body composition. Dual-energy X-ray absorptiometry (DXA), using a low-energy X-ray source, is now more widely used because of its greater accuracy. This technique measures three compartments of the body: bone mass, lean body mass, and fat mass. Each of these tissues varies in density, and therefore they attenuate the energy beams differently. The use of dual energy beams allows for solution of three tissue compartments. DXA involves radiation exposure, although the exposure is extremely low (3.5 mr). Whole body estimates of body composition for infants, children, and adolescents can be obtained in less than 5 minutes (Figure 13-3). For subjects with metal implants or who are unable to complete a measurement without movement, the quality of DXA-derived body composition estimates is suspect. However, since variability in bone mineral density is a primary source of error in the estimation of the density of fat-free mass, DXA measurements are more accurate in estimating fat-free mass than in techniques that use a two-compartment model, such as densitometry. Compared to the bioelectrical and anthropometric methods of body composition assessment described previously, it has the added advantage of being independent of sample-based prediction equations.

Neutron Activation

In vivo neutron activation analysis is a very specialized method for measuring atomic-level components of the body. The major elements are Ca, C, Cl, H, N, Na, O, and P; trace elements of Al, Cd, Cu, Fe, and Si are also measured. Only a handful of research centers worldwide use neutron activation analysis, and it is not an acceptable technique for infants and children. However, it is extremely accurate and the only in vivo method for this kind of body composition assessment. While resting in a shielded chamber, the subject is bombarded with a dose of fast neutrons. The neutrons interact with the nuclei of the element or elements of interest (e.g., carbon or nitrogen), forming unstable isotopes that emit gamma radiation. The whole body gamma radiation counter then can determine the total quantity of the element in the body.[22]



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oJun 8 13:47 2001  [333 x 152]
  Hologic QDR-2000 (S/N 2219)
Enhanced Array Whole Body V8.25A:1

 Head assumes 17.0% brain fat
 LBM 73.2% water
Region     Fat    Lean+BMC   % Fat
        (grams)   (grams)     (%)
------- -------- --------- -------
 L Arm   1884.7   1764.4   51.6
 R Arm   1703.7   2299.3   42.6
 Trunk  13468.2  19037.4   41.4
 L Leg   5671.8   7415.4   43.3
 R Leg   6022.7   7692.0   43.9
SubTot  28751.1  38208.6   42.9
  Head    939.6   4113.8   18.6
 TOTAL  29690.7  42322.4   41.2
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HOLOGIC

FIGURE 13-3 Whole body scan using dual-energy X-ray absorptiometry to determine bone mineral mass, lean tissue mass, and fat mass.

Computerized Axial Tomography

Computerized axial tomography (CT) scans give three-dimensional images for regional analysis of body composition. While whole-body analysis is possible, it is quite impractical due to the expense, time, and radiation exposure involved with the technique. CT systems use a X-ray source and detector, and the attenuation of the X rays is used to construct the image of the tissue area. Multiple "slices" can be used to construct larger areas of the body. CT scans have been used effectively to estimate visceral adipose tissue, organ volumes, the area and density of vertebral bodies, and skeletal muscle mass. Peripheral CT devices are also available for imaging the bone (especially cortical versus trabecular bone), muscle, and fat at appendicular sites, such as the distal radius or tibia.

BODY COMPOSITION AND GROWTH

Infancy

The water content of the human fetus is high and about 75% of body weight at birth. Following birth, there are rapid changes in hydration. During the first few days of life, the full-term infant loses 5–10% of body weight, much of which is water (mainly extracellular). The extracellular water as a percent of body weight declines from 44.5% on the first day of life, to 18.7% by 10–15 years old. Intracellular water increases from 34 to 46.7% over the same time period.[23] The composition of lean tissue is significantly affected. At birth, the hydration of fat-free mass is approximately 80–82% and declines to 78% by 2 years old. Hydration of free-fat mass continues to decline at a slower pace, as indicated by the hydration constants in Table 13-5.

Human infants are born with a large head relative to the size of the total body. At birth, the brain represents 13% of total body weight (compared to 2% of total body weight in adulthood). Other organs, such as the heart, lung, and liver, also constitute a large percentage of infant body mass. Therefore, organ tissue makes a greater contribution to body weight and lean body mass during infancy. As other parts of the body grow, these relative proportions change, as shown in Figure 13-4.[24]

Infancy is one of the most rapid periods of growth during the human life cycle. Weight and length increase rapidly and birth weight is usually doubled by 4–5 months old. Fat and fat-free mass increase and fat as a percentage of total body weight peaks at about 3–6 months. A recent investigation showed that, by 6 months old, average percent body fat for boys was 29.1 ± 4.7 and for girls it was 32.0 ± 4.4%.[25] Boys also had significantly greater fat-free mass, total body water, total body potassium, and bone mineral content than girls throughout infancy. Thus, girls and boys differ in body composition, even during infancy. In addition, feeding patterns influenced the changes in the amount and relative proportions of the fat and fat-free mass compartments in these infants; breast-fed infants were not as heavy

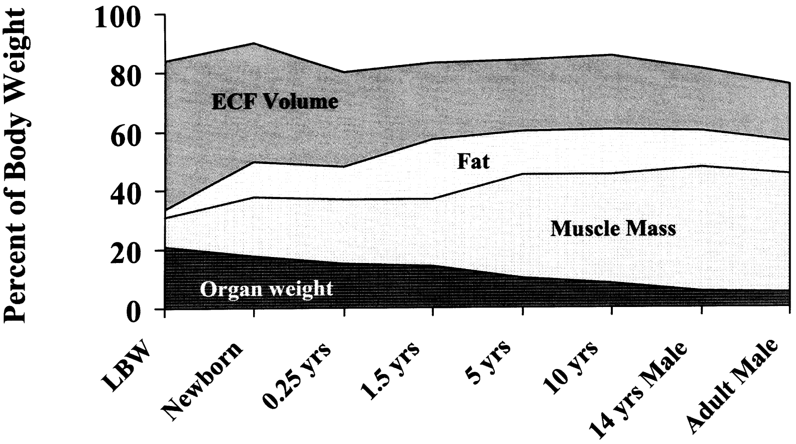

FIGURE 13-4 Changes in the relative proportions of body components with growth and maturation. (Source: Adapted from Halliday.[24])

and had less fat at 9 and 15 months old than formula-fed babies.[26] However, recent data suggests that differences in growth between breast-fed and formula-fed babies do not persist into childhood.[27]

Childhood

During childhood, growth proceeds at a far slower pace than in infancy and adolescence. Likewise, growth in body compartments and changes in chemical composition also proceed at an unremarkable pace. During this period, sex differences in body fatness are apparent, with girls, on average, having a higher percent body fat than boys even prior to the onset of sexual maturation.

The midchildhood growth spurt, which occurs in many children around 6–8 years old, is a small increase in the rate of gain in weight, height, and body breadth. At approximately the same age, the body mass "rebound" occurs. The body mass index declines from early childhood (1 year old) reaching a nadir at about 5–6 years old. The BMI then begins to increase, continuing through adolescence and into adulthood. The "rebound" refers to the turn around in BMI.[28] Children who experience this rebound at an earlier age are more likely to have a higher BMI and become obese.

Adolescence

The onset of sexual maturation is associated with profound and rapid changes in the body compartments and chemical maturation. These changes are primarily due to the effect of gonadal steroids on the tissues (muscle, fat, bones, and organs).

Although sex differences in body composition are present during infancy and childhood, they become far more pronounced during adolescence.

In part, the body composition changes are due to the rapid increases in body mass associated with the adolescent growth spurt. Organs such as the heart and brain also increase in size during this period. Fat and fat-free mass change in absolute amount, relative proportion, and anatomic distribution. Girls gain steadily in fat and fat-free mass through childhood, but more rapid gains in these compartments and in percent body fat are associated with puberty. Growth of breast tissue contributes to the gain in overall fat mass and percent body fat, as does the gradual attainment of a mature female fat distribution, with additional fat at the hips and thighs. Many boys experience a prepubertal fat spurt. The subsequent adolescent growth spurt in boys results in significant gains in lean body mass, reductions in fat at the extremities (such as at the triceps skinfold site), and increasing fat deposition at the trunk (such as at the subscapular site).

Bone mineralization also changes significantly during adolescence. Approximately 40% of peak bone mass (the maximum amount of bone in the body during one's lifetime) is attained during adolescence. In part, this is due to the growth of the skeleton and the expansion of bone mass. The density of bones also change during adolescence. Figure 13-5 shows the change in bone mass relative to the growth spurt in height.[29] The lag time between the spurts in height and bone mass represents the increase in bone mass that follows the increase in height.

Adulthood and Senescence

Body mass and composition change during adulthood, although generally the changes are not as pronounced as during adolescence or infancy. In most westernized countries, adults continue to gain weight through adulthood. The age-associated increase in BMI suggests that this is mainly increased fatness. Nonwesternized societies do not experience similar gains in adult weight or BMI, although with increasing modernization, this trend is apparent in some locales. Toward the end of life, there is often a loss of body weight, particularly of the fat-free mass compartment, that can be due to underlying illness, reduced physical activity, poor nutritional intake, and poor nutrient absorption.

In women, changes in reproductive status (pregnancy, lactation, and menopause) are also associated with rapid and significant shifts in body composition. Fluctuations in bone and fat mass can be particularly pronounced, due to the effect of hormonal changes on these body compartments. During pregnancy, women gain in total body water (4–6 kg) and fat (2–4 kg), in addition to the gains associated with the fetus, placenta, and amniotic fluid. During the teenage years, the body composition changes associated with pregnancy can include the combined effects of pregnancy and ongoing growth of the mother, simultaneously. For these very young women, pregnancy may have long-lasting effects on body composition in terms of increased adiposity and reduced bone mass.[30] Loss of bone mass and density are associated with pregnancy and lactation, however recovery of bone mass

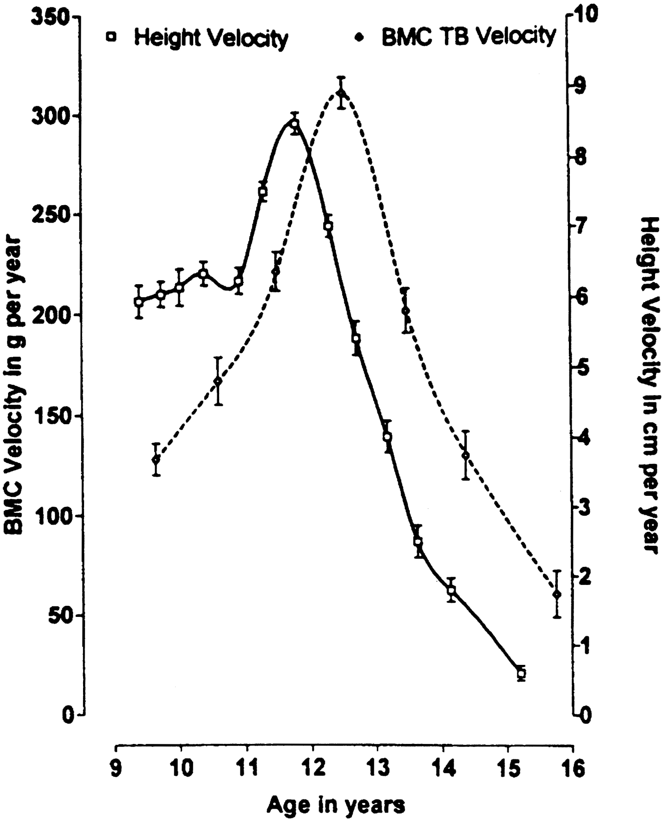

FIGURE 13-5 Peak velocity in bone mineral mass (BMC) accrual of the total body (TB) compared to height velocity in girls. (Source: McKay et al.[29])

appears to be fairly rapid and complete with the onset of post-partum menses and cessation of lactation.

Menopause is another period of body composition change for women. There is an increase in fatness and changes in fat distribution following the midlife hormonal changes.[31,32] Skeletal changes also occur. In the years just prior to and following the onset of menopause, there is significant bone loss under natural conditions (i.e., without hormone replacement therapy). One longitudinal study estimated a 10% loss of bone density in the lumbar spine region.[33] The loss of trabecular bone, especially of the spine, can be particularly profound.[34] In premenopausal women, the trabecular bone loss has been estimated at –0.45 mg/ml per year; for perimenopausal women it was –4.39 mg/ml per year, and for postmenopausal women was –1.99 mg/ml per year. These changes can result in osteoporosis and increased risk of hip fracture with its associated mortality risk.

BODY COMPOSITION IN HEALTH AND DISEASE

Body composition is influenced by heredity and the environment. In turn, body composition can have lifelong consequences in terms of overall health, physical activity patterns, and work productivity. Several examples of the importance of body composition are described.

Chronic Undernutrition, Physical Activity, and Work Capacity

Chronic undernutrition results in smaller body size and delayed maturation. Provided the undernutrition is chronic and not acute, weight-for-height relationships, such as BMI, are preserved in children. However, in the long run, chronic undernutrition can result in lower physical activity levels and work productivity. For example, among school-aged boys in Colombia, the group of poorly nourished boys had less spontaneous physical activity than adequately nourished boys.[35] Similarly, among children with sickle cell disease who have reduced fat-free mass and fat mass, total energy used for physical activity was lower than healthy controls.[36] In studies of populations at risk for chronic undernutrition, there is a significant, positive association between BMI (a measure of current nutritional status) and height (an indicator of nutritional history) and the amount of time devoted to work. In other words, higher levels of both BMI and stature were correlated with an increased capacity to carry out work.[37]

Body Composition and Diet

Much is still to be learned about the relationship between body composition and diet. The essential nutrients required for normal growth and cell functioning assure normal body composition. Clearly, when severe nutrient deficiencies exist, body composition is altered. For example, severe protein malnutrition leads to muscle wasting and altered fluid balance. Milder nutrient deficiencies may have direct or indirect effects. Inadequate calcium intake results in inadequate bone mineralization, thereby lowering total body bone mineral mass and the density of the bone fraction of the fat-free mass and increasing the risk of fracture later in life. Iron-deficiency anemia in children is associated with lethargy and poor cognitive development, which in turn may limit a child's engagement in usual childhood physical activities that would promote muscle and bone growth.

The association between diet patterns and body composition is even less well defined. On average, vegetarians have less body fat then omnivores, and vegans, who exclude all animal products from their diet, are leaner still than both vegetarians and omnivores. Vegetarians and vegans are also known to have lower blood pressure and cholesterol. It is uncertain whether these health effects are directly related to diet or mediated by differences in body composition. Less is known about other dietary patterns, such as very high protein, fat, or carbohydrate intake because of the difficulties of conducting long-term studies where physical activity, energy intake, and health status are comparable across groups.

Health Consequences of Obesity

Excess adiposity is reaching epidemic proportions among children and adults in many industrialized and industrializing nations. Among children, obesity is defined as having a BMI greater than the 95th percentile for age and sex, and overweight is defined as having a BMI between the 85th and 95th percentiles for age and sex. Not only is the prevalence of obesity and overweight increasing, but the magnitude of the excess weight in obese children is also greater. Results from the most recent National Health and Nutrition Examination Survey in the United States[38] showed that 10.9% of children were obese (above the 95th percentile for BMI) and 22% of children were above the 85th percentile for BMI. Overweight and obesity is not simply due to increased size of the fat compartment of the body. Increased lean body mass and bone mass also occurs in obesity.

The health consequences of overweight and obesity in childhood and adolescence are not well documented. In adults, very low BMI levels are associated with increased risk of mortality from digestive and pulmonary diseases, but as BMI increases above 25 kg/m^2, mortality rates from cardiovascular disease, gall bladder disease, and diabetes mellitus increase (Figure 13-6).[39,40] In children, the health risks associated with obesity include bone and joint disease, increased blood pressure and serum cholesterol, and insulin resistance as well as increased risk of non-insulin-dependent diabetes.[41] But most believe the greatest health risk of childhood obesity is due to the increased risk of adult obesity among this subgroup of

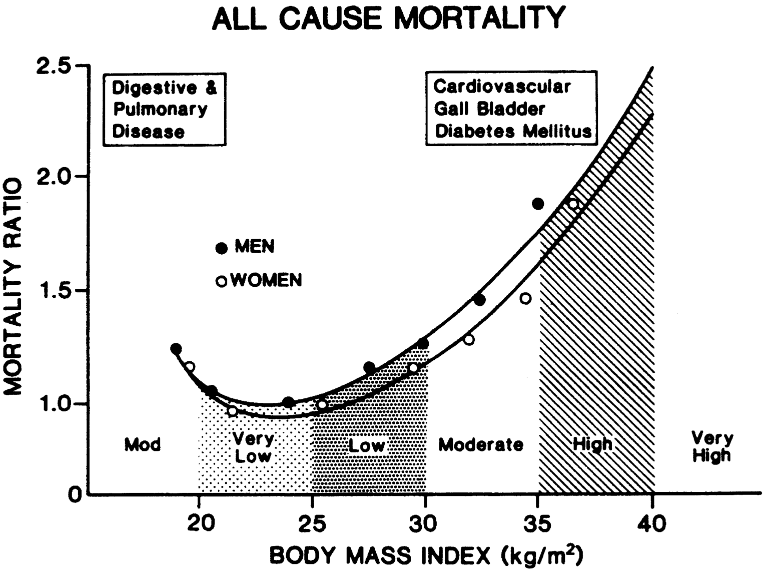

FIGURE 13-6 Relationship between body mass index and mortality in adults. (Source: Gray.[39])

children. Few unbiased longitudinal studies are available to determine the association between childhood and adult obesity. The risk of being an obese adult is greater for obese adolescents than for obese adults.[42] Obesity is associated with increased risk of heart disease, hypertension, stroke, coronary heart disease, non-insulin-dependent diabetes, lipid disorders, gallbladder disease, orthopedic problems, sleep apnea, and some cancers. Although treatment of these associated health problems rarely results in weight loss, modest reductions in weight can result in improvements in some parameters, such as blood pressure and lipid levels.[43,44]

Fat Distribution as a Correlate of Diseases

In addition to the total and relative amount of fat, the distribution of fat on the body represents an independent risk factor for certain diseases. In particular, the tendency to accumulate fat on the upper trunk of the body, as opposed to the hips or limbs, is associated with non-insulin-dependent diabetes, hypertension, and gall bladder disease. This fat distribution pattern is referred to as an *android* distribution, since men tend to gain fat on their trunk. The *gynoid* distribution, with relatively greater fat on the hips, thighs, and arms, is more typical of women. However, these fat distribution patterns can be found in people of both genders. Both adiposity and fat patterning were associated with cardiovascular risk factors (lipid profiles and blood pressure) in a large, multiethnic sample of boys and girls participating in the National Heart, Lung, and Blood Institute Growth and Health Study.[45,46]

Physical Activity and Body Composition

As noted already, body composition, fatness, and fat patterning have a strong hereditary component. However, behavioral and lifestyle factors, most notably physical activity, can influence body composition. Physical activity, especially weight-bearing activity, is important for growth and maintenance of the muscle and bone compartments. The energy demands of intense physical activity also influence fatness levels. These are illustrated most easily at the extremes of physical activity. Children with severe quadriplegic cerebral palsy, who are unable to walk, have markedly reduced growth of lower limbs, reduced muscle and fat stores, and low bone mineral content and bone density. Children with diplegic or hemiplegic cerebral palsy have deficits commensurate with their ability to ambulate and bear weight. Even among previously healthy individuals with normal physical activity patterns, prolonged bed rest results in muscle and bone atrophy. Astronauts in space living in a weightless environment experience similar problems.

Milder limitations of physical activity may promote increased fatness. Increased hours of television viewing and reduction in hours of physical education classes are associated with increased risk of overweight in children in the United States. However, increased body mass, in itself, increases the weight-bearing stress of usual activities and is thereby associated with increased total body lean mass. Therefore, among overweight and obese children, both fat-free mass and fat mass are often increased. At the other extreme, intense physical activity is associated with reduced fatness. Body composition profiles vary by different sports activities. Long-distance running and ballet dancing, and other activities known for prolonged and intense training, are associated with significantly reduced fat mass. In females, these athletes often become amenorrheic and develop osteoporosis related to estrogen insufficiency. Sports that involve resistance training generally promote higher bone density.

CONCLUSION

The composition of the human body is regulated by genes but is sensitive to environmental, behavioral, and nutritional factors. Interaction between the genetic and nongenetic influences contribute to the variability in body composition observed within and between populations. Body composition is also an integral part of human growth, maturation, and senescence and has a wide range of health implications. A broad array of body composition assessment techniques can be used in clinical, research, and field settings to further understand the life-cycle changes in body composition and their role in health and disease.

REFERENCES

1. Wang ZM, Pierson RN, Heymsfield SB. The five-level model: A new approach to organizing body composition research. Amer J Clin Nutr. 1992;56:19–28.
2. Frisch H. Growth hormone and body composition in athletes. J Endocrinol Invest. 1999; 22(5 Suppl):106–109.
3. Bouchard C. Genetic influences on human body composition and physique. In: Roche AF, Heymsfield SB, Lohman TG (eds). Human Body Composition. Champaign, IL: Human Kinetics, 1996:305–327.
4. Malina RM. Regional body composition: Age, sex, and ethnic variation. In: Roche AF, Heymsfield SB, Lohman TG (eds). Human Body Composition. Champaign, IL: Human Kinetics, 1996:217–255.
5. Malina RM, Huang YC, Brown KH. Subcutaneous adipose tissue distribution in adolescent girls of four ethnic groups. Int J Obes Relat Metab Disord. 1995;19(11):793–797.
6. Schutte JE, Townsend EJ, Hugg J, Shoup RF, Malina RM, Blomqvist CG. Density of lean body mass is greater in blacks than in whites. J Appl Physiol. 1984;56(6):1647–1649.
7. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys, 1963 to 1991. Arch Pediatr Adolesc Med. 1995;149(10):1085–1091.
8. Martorell R, Kettel Khan L, Hughes ML, Grummer-Strawn LM. Overweight and obesity in preschool children from developing countries. Int J Obes Relat Metab Disord. 2000;24(8):959–967.
9. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM. CDC Growth Charts—United States. Advance Data from Vital and Health Statistics, No. 314. National Center for Health Statistics, June 8, 2000 (revised).
10. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: International survey. Brit Med J. 2000;320(7244):1240–1243.
11. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Amer J Clin Nutr. 1981;34:2540–2545.

12. Sentongo TA, Semeao EJ, Piccoli DA, Stallings VA, Zemel BS. Growth, body composition and nutritional status in children and adolescents with Crohn's disease. J Pediatr Gastroenterol Nutrit. 2000;31(1):33–40.
13. Slaughter MH, Lohman TG, Boileau RA, Horswill CA, Stillman RJ, Van Loan MD, et al. Skinfold equations for estimation of body fatness in children and youth. Hum Biol. 1988;60(5):709–723.
14. Brook CGD. Determination of body composition of children from skinfold measurements. Arch Dis Child. 1971;46:182.
15. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Brit J Nutrit. 1967;21:681.
16. Zemel BS, Riley ER, Stallings VA. Evaluation of methodology for nutritional assessment in children: anthropometry, body composition and energy expenditure. Ann Rev Nutrit. 1997;17:211–235.
17. Frisancho A. Anthropometric Standards for the Assessment of Growth and Nutritional Status. Ann Arbor: University of Michigan Press, 1990.
18. Going SB. Densitometry. In: Roche AF, Heymsfield SB, Lohman TG (eds). Human Body Composition. Champaign, IL: Human Kinetics, 1996:3–23.
19. Lohman TG. Assessment of body composition in children. Pediat Exercise Science. 1989;1(1):19–30.
20. Schoeller D. Hydrometry. In: Roche AF, Heymsfield SB, Lohman TG (eds). Human Body Composition. Champaign, IL: Human Kinetics, 1996:25–43.
21. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: Advances in models and methods. Ann Rev Nutrit. 1997;17:527–558.
22. Ryde SJS. In vivo neutron activation analysis: past, present and future. In: Davies PSW, Cole TJ (eds). Body Composition Techniques in Health and Disease. Society for the Study of Human Biology Symposium 36. Cambridge: Cambridge University Press, 1995.
23. Shepard RJ. Body Composition in Biological Anthropology. Cambridge Studies in Biological Anthropology. Cambridge: Cambridge University Press, 1991.
24. Holliday MA. Body composition and energy needs during growth. In: Falkner F, Tanner JM (eds). Human Growth. New York: Plenum, 1986.
25. Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ. Body composition during the first two years of life: An updated reference. Pediatr Res. 2000;47:578–585.
26. Butte NF, Wong WW, Hopkinson JM, Smith EO, Ellis KJ. Infant feeding mode affects early growth and body composition. Pediatr. 2000;106(6):1355–1366.
27. Hediger ML, Overpeck MD, Ruan WJ, Troendle JF. Early infant feeding and growth status of US-born infants and children aged 4–71 months: Analyses from the third National Health and Nutrition Examination Survey, 1988–1994. Amer J Clin Nutrit. 2000;72(1):159–167.
28. Rolland-Cachera MF, Deheeger M, Bellisle F, Sempe M, Guilloud-Bataille M, Patois E. Adiposity rebound in children: a simple indicator for predicting obesity. Amer J Clin Nutrit. 1984; 39(1):129–135.
29. McKay HA, Bailey DA, Mirwald RL, Davison KS, Faulkner RA. Peak bone mineral accrual and age at menarche in adolescent girls: A 6-year longitudinal study. J Pediatr. 1998;133:682–687.
30. Hediger ML, Scholl TO, Schall JI. Implications of the Camden Study of adolescent pregnancy: Interactions among maternal growth, nutritional status, and body composition. Ann NY Acad Sci. 1997;817:281–291.
31. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Menopause-related changes in body fat distribution. Ann NY Acad Sci. 2000;904:502–506.
32. Poehlman ET, Tchernof A. Traversing the menopause: Changes in energy expenditure and body composition. Coron Artery Dis. 1998;9(12):799–803.
33. Recker R, Lappe J, Davies K, Heaney R. Characterization of perimenopausal bone loss: A prospective study. J Bone Miner Res. 2000;15(10):1965–1973.
34. Block JE, Smith R, Gluer CC, Steiger P, Ettinger B, Genant HK. Models of spinal trabecular bone loss as determined by quantitative computed tomography. J Bone Miner Res. 1989;4(2):249–257.
35. Spurr GB, Reina JC. Patterns of daily energy expenditure in normal and marginally undernourished school-aged Colombian children. Euro J Clin Nutrit. 1988;42(10):819–834.

36. Barden EM, Zemel BS, Kawchak DA, Goran MI, Ohene-Frempong K, Stallings VA. Total and resting energy expenditure in children with sickle cell disease. J Pediatr. 2000;136:73–79.
37. Kennedy E, Garcia M. Body mass index and economic productivity. Euro J Clin Nutrit. 1994;48(Suppl 3):S45–S53; discussion S53–S55.
38. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys, 1963 to 1991. Arch Pediatr Adolesc Med. 1995;149(10):1085–1091.
39. Gray DS. Diagnosis and prevalence of obesity. Med Clin North Amer. 1989;73:1–13.
40. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999;341:1097–1105.
41. Dietz WH, Robinson TN. Assessment and treatment of childhood obesity. Pediatr Rev. 1993;14(9):337–344.
42. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med. 1992;327(19):1350–1355.
43. Wadden TA, Anderson DA, Foster GD. Two-year changes in lipids and lipoproteins associated with maintenance of a 5% to 10% reduction in initial weight: Some findings and questions. Obes Res. 1999;8(2):170–178.
44. Van Gaal LF, Wauters MS, De Leeuw IH. The beneficial effects of modest weight loss on cardiovascular risk factors. Int J Obes Relat Metab Disord. 1997;21(Suppl 1):S5–S9.
45. Morrison JA, Sprecher DL, Barton BA, Waclawiw MA, Daniels SR. Overweight, fat patterning, and cardiovascular disease risk factors in black and white girls: The National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr. 1999;135(4):458–464.
46. Morrison JA, Barton BA, Biro FM, Daniels SR, Sprecher DL. Overweight, fat patterning, and cardiovascular disease risk factors in black and white boys. J Pediatr. 1999;135(4):451–457.

14

THE EVOLUTION OF HUMAN GROWTH

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GROWTH AND EVOLUTION

If there is a "secret" to life, it is hidden in the process that converts a single cell, with its complement of deoxyribonucleic acid (DNA), into a multicellular organism composed of hundreds of different tissues, organs, behavioral capabilities, and emotions. That process is no less wondrous when it occurs in an earthworm, a whale, or a human being. In this chapter, I focus on the process of human growth and development; however, the reader must be aware that much of what we know about human growth is derived from research on nonhuman animals. The two reasons for this are ethical limits on the kind of experimental research that may be performed on human beings and the evolutionary history that connects all living organisms.

Many growth processes that occur in humans are identical to those in other species and attest to a common evolutionary origin. Powerful evidence for the common evolutionary origin of the eye came in 1995 with the discovery of a "master-control gene" for eye growth and development.[1] This gene is common to species as diverse as marine worms, squid, fruit flies, mice, and humans. Other organs, and the mechanisms that control their growth and development, are also shared among many diverse species. Some events in the human life cycle may be unique, such as the adolescent growth spurt in height and menopause, and they attest to the ongoing evolution of our species.

Biological evolution is the continuous process of genetic adaptation of organisms to their environments. Natural selection determines the direction of evolutionary change and operates by differential mortality between individual organisms prior to reproductive maturation and by differential fertility of mature organisms. Thus, genetic adaptations that enhance the survival of individuals to reproductive age and increase the production of similarly successful offspring increase in frequency in the population. The unique stages and events of human growth and development evolved because they conferred reproductive advantages to our species.

LIFE HISTORY AND STAGES OF THE LIFE CYCLE

Life history might be defined as the strategy an organism uses to allocate its energy toward growth, maintenance, reproduction, raising offspring to independence, and avoiding death. For a mammal, it is the strategy of when to be born, when to be weaned, how many and what type of prereproductive stages of development to pass through, when to reproduce, and when to die. Living things on earth have greatly different life history strategies, and understanding what shapes these histories is one of the most active areas of research in whole-organism biology.

Anthropologists have become increasingly interested in explaining the significance of human life history. This interest is due to the discovery that the human life cycle stands in sharp contrast to other species of social mammals, even other primates. Anthropological theory needs to explain how humans successfully combined a vastly extended period of offspring dependency and delayed reproduction with helpless newborns, a short duration of breast feeding, an adolescent growth spurt, and menopause. A central question is, did these characteristics evolve as a package or a mosaic? The present evidence suggests that human life history evolved as a mosaic and may have taken form over more than a million years.

Understanding the human condition requires a comparative approach, and here I restrict such comparisons to the mammals. We can use the same criteria to describe and define the stages of the life cycle for nonhuman mammals and the human species. Recent work in mammalian life history and its evolution focuses on the period of the life cycle from birth to adulthood. Researchers are especially interested in changes in the rate of growth and the timing of the onset of reproductive maturation. The majority of mammals progress from infancy to adulthood seamlessly, with no intervening stages, and puberty occurs after the peak velocity of their postnatal growth. This pattern of postnatal growth is illustrated in Figure 14-1, using data for the mouse. Highly social mammals such as wolves, wild dogs, lions, elephants, and the primates (e.g., the baboon, Figure 14-2) postpone adulthood by inserting a period of juvenile growth and behavior between infancy and adulthood.

Most mammalian biologists define *infancy* as the stage of life when the offspring are fed by nursing. Adulthood is the stage of life when the individual is capable of reproduction. *Juveniles* may be defined as "prepubertal individuals that are no longer dependent on their mothers (parents) for survival."[2 (p. 236)] Some debate ensues as to the function of the juvenile stage for social mammals. The traditional

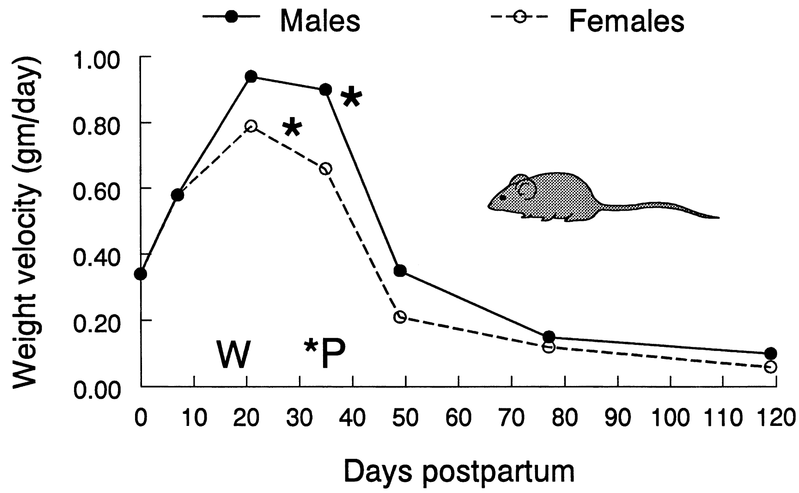

FIGURE 14-1 Velocity curves for weight growth in the mouse. In both sexes puberty (*; vaginal opening for females or spermatocytes in testes of males) occurs just after weaning (W) and maximal growth rate. Weaning takes place between days 15 and 20. Sexual maturity follows weaning by a matter of days. (Source: Adapted from Tanner.[24])

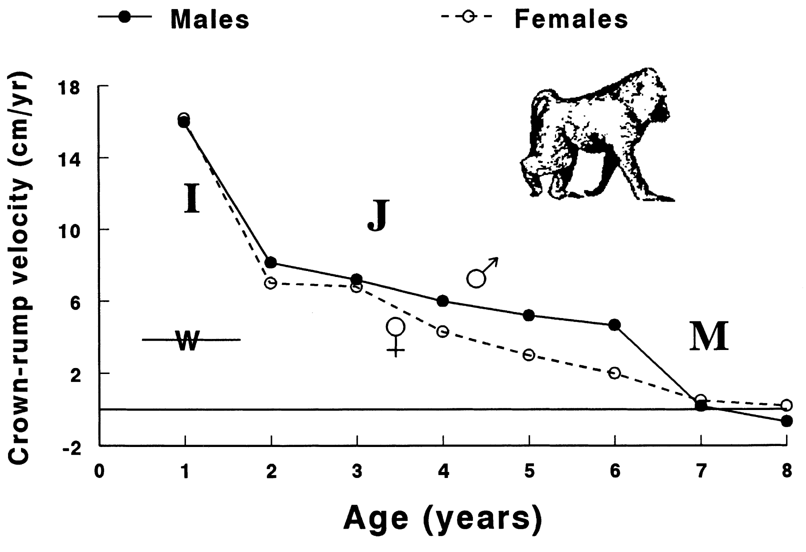

FIGURE 14-2 Baboon crown–rump length velocity. Letters indicate the stages of growth as in Figure 14-1. Weaning (W) may take place anytime between 6 and 18 months. (Source: Adapted from Coelho.[25])

"learning hypothesis" is that the juvenile period allows for the extended period of brain growth and learning necessary for success in the species of group-living social mammals: the social hierarchy, feeding skills such as hunting, and reproductive skills. A recent corollary to the learning hypothesis is the "starvation aversion hypothesis" proposed by Janson and Van Schaik.[3] Juveniles must forage for their own food, a skill that must be practiced until mature levels of success are achieved. Much of the foraging of juveniles is in competition with adults. This competition becomes clear during times of food scarcity, when juvenile primates die in greater numbers than infants or adults. The point is that a slow-growing juvenile requires less food input than a fast-growing infant, and the juvenile may practice feeding skills with less risk of starvation during the learning period.

Another possible explanation for a juvenile stage for social mammals may be called the *dominance hypothesis*. Research with wild and captive primates shows that high-ranking individuals in the social hierarchy can suppress and inhibit the reproductive maturation of low-ranking individuals. The inhibition may be due to the stress of social intimidation acting directly on the endocrine system or secondary to inadequate nutrition due to feeding competition. Juveniles are almost always low-ranking members of primate social systems. In the past, individuals with slow growth and delayed reproductive maturation after infancy may have survived to adulthood more often than individuals with rapid growth and maturation, and thus juvenile stage may have evolved. Whatever the cause, Alexander[4] points out that, in broad perspective, "juvenile life has two main functions: to get to the adult stage without dying and to become the best possible adult." Adding a juvenile stage must have served this purpose well.

HUMAN LIFE STAGES

During human evolution, childhood and adolescence were added as new life stages. This means that humans have five life stages after birth: infancy, childhood, juvenile, adolescent, and adulthood. These new stages presumably add additional security and value to the whole of human life history. Universally, human females who live long enough experience menopause, another new stage for primates and an event that may mark the passage from one phase of adult life to another. To visualize the amount and rate of growth that takes place during each of these stages, the growth in height (or length) for normal boys and girls is depicted in Figure 14-3; growth in weight follows very similar curves. The stages of growth are also outlined in Table 14-1. In Figure 14-3, the distance curve of growth, that is, the amount of growth achieved from year to year, is labeled on the right *y*-axis. The velocity curve, which represents the rate of growth during any single year, is labeled on the left *y*-axis. Below the velocity curve are symbols that indicate the average duration of each stage of development. Clearly, changes in growth rate are associated with each stage of development. Each stage also may be defined by characteristics of the dentition, changes related to meth-

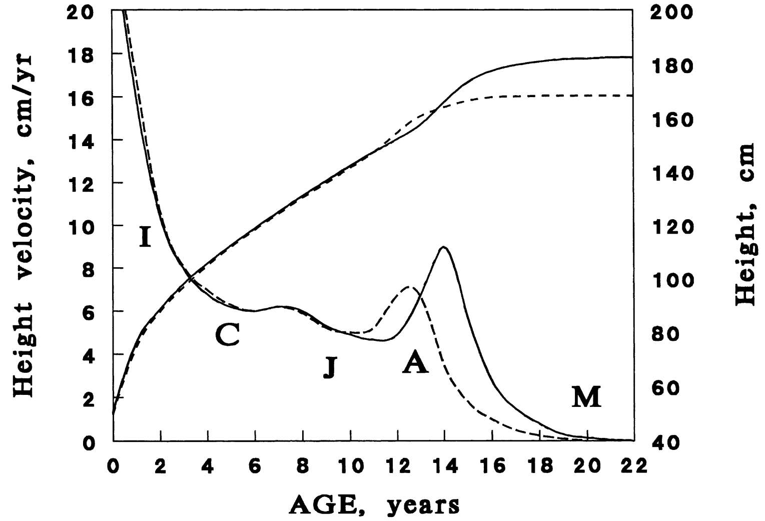

FIGURE 14-3 Idealized mean velocity and distance curves of growth in height for healthy girls (dashed lines) and boys (solid lines) showing the postnatal stages of the pattern of human growth. Note the spurts in growth rate at midchildhood and adolescence for both girls and boys. The postnatal stages: I, infancy; C, childhood; J, juvenile; A, adolescence; M, mature adult. (Source: Data from Prader[26] and Bock and Thissen.[27])

ods of feeding, physical and mental competencies, or maturation of the reproductive system and sexual behavior.

Infancy

Infancy is characterized by the most rapid velocity of growth of any of the postnatal stages. The infant's rate of growth is also characterized by a steep decline in velocity or deceleration. As for all mammals, human infancy is the period when the mother provides all or some nourishment to her offspring via lactation or some culturally derived imitation of lactation. During infancy, the deciduous dentition (the so-called milk teeth) erupts through the gums. Human infancy ends when the child is weaned from the breast, which in preindustrialized societies occurs between 24 and 36 months of age. By this age, all the deciduous teeth have erupted, even for very late-maturing infants.

Motor skills (i.e., what a baby can do physically) develop rapidly during infancy. There is a similar progression of changes in the problem-solving, or cognitive, abilities of the infant. The development of the skeleton, musculature, and the nervous system account for all these motor and cognitive advancements. The rapid growth of the brain, in particular, is important. Later in this chapter, I explain how the evolution of the relatively large human brain has influenced the total pattern of

TABLE 14-1 Stages in the Human Life Cycle

Stage	Growth Events and Duration (Approximate or Average)
Prenatal life	
Fertilization	
First trimester	Fertilization to 12th week: embryogenesis
Second trimester	Fourth through sixth lunar month: rapid growth in length
Third trimester	Seventh lunar month to birth: rapid growth in weight and organ maturation
Birth	
Postnatal life	
Neonatal period	Birth–28 days: extrauterine adaptation, most rapid rate of postnatal growth and maturation
Infancy	Month 2–end of lactation, usually by 36 months: rapid growth velocity but with steep deceleration in growth rate, feeding by lactation, deciduous tooth eruption, many developmental milestones in physiology, behavior, and cognition
Childhood	Years 3–7: moderate growth rate, dependency on older people for care and feeding, midgrowth spurt, eruption of first permanent molar and incisor, cessation of brain growth by end of stage
Juvenile	Years 7–10 for girls, 7–12 for boys: slower growth rate, capable of self-feeding, cognitive transition leading to learning of economic and social skills
Puberty	Occurs at end of juvenile stage and is an event of short duration (days or a few weeks): reactivation of central nervous system for sexual development, dramatic increase in secretion of sex hormones
Adolescence	The stage of development that lasts for 5–10 years after the onset of puberty: growth spurt in height and weight, permanent tooth eruption almost complete, development of secondary sexual characteristics, sociosexual maturation, intensification of interest in and practice of adult social, economic, and sexual activities
Adulthood	
Prime and transition	From 20 years old to end of childbearing years: homeostasis in physiology, behavior, and cognition; menopause for women by age 50
Old age and senescence	From end of childbearing years to death: decline in the function of many body tissues or systems

human growth and development. I point out that the human brain grows rapidly during infancy, much more rapidly than almost any other tissue or organ of the body (Figure 14-4).

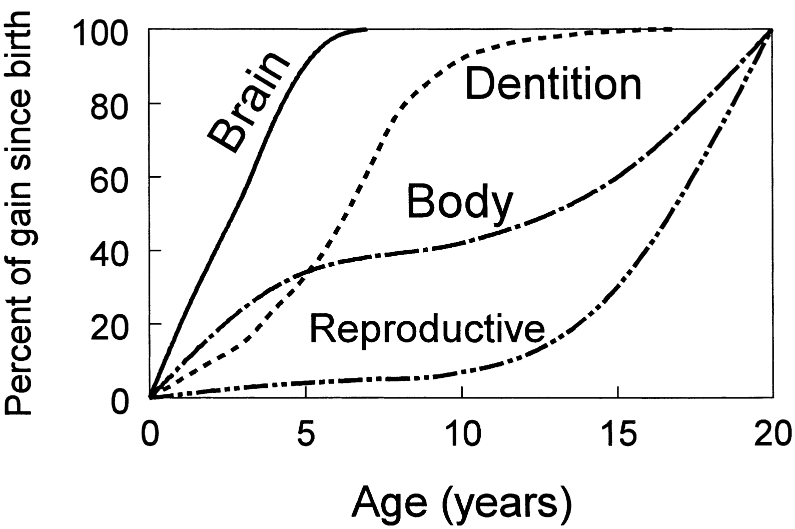

FIGURE 14-4 Growth curves for different body tissues. The Brain curve is for total weight of the brain.[28] The Dentition curve is the median maturity score for girls based on the seven left mandibular teeth (I1, I2, C, PM1, PM2, M1, M2).[29] The Body curve represents growth in stature or total body weight, and the Reproductive curve represents the weight of the gonads and primary reproductive organs.[30]

Childhood

The childhood stage follows infancy, encompassing the ages of about 3–7 years. *Childhood* may be defined by its own pattern of growth, feeding behavior, and motor and cognitive development. The growth deceleration of infancy ends at the beginning of childhood, and the growth rate levels off at ±5 cm) per year. This leveling-off in growth rate is unusual for mammals, because almost all other species continue a pattern of deceleration after infancy (Figures 14-1 and 14-2).

This slow and steady rate of human growth maintains a relatively small-sized body during the childhood years. In terms of feeding, children are weaned from the breast or bottle but still depend on older people for food and protection. Most mammalian species move from infancy, and its association with dependence on nursing, to a stage of independent feeding. Postweaning dependency is, by itself, not a sufficient criterion to define *human* childhood, as several species of social mammals, especially carnivores (such as lions, wild dogs, and hyenas) and some species of primates also have this dependency. Human children do, of course, learn how to find and prepare food, but a suite of features defines the childhood stage. Not all of these features are found for the social carnivores and nonhuman primates. Human children require specially prepared foods because of the immaturity of their dentition, the small size of their stomachs and intestines, and the rapid growth of their brain (Figure 14-4). Again, I emphasize that the human brain is especially important. The newborn uses 87% of its resting metabolic rate (RMR) for brain growth and function. By 5 years old, the percent RMR usage is still high at 44%, whereas in the adult human, the figure is between 20 and 25% of RMR. At comparable stages of development, the RMR values for the chimpanzee are about 45, 20, and 9%, respectively.

The human constraints of immature dentition and small digestive system necessitate a childhood diet that is easy to chew and swallow and low in total volume. The child's relatively large and active brain, almost twice the size of an adult chimpanzee's brain, requires that the low-volume diet be dense in energy, lipids, and proteins. Children do not yet have the motor and cognitive skills to prepare such a diet for themselves. Children are also especially vulnerable to predation and disease and so require protection. Children will not survive in *any* society if deprived of the care provided by older individuals. So-called wolf children and even "street children," who are sometimes alleged to have lived on their own, are either myths or not children at all. A search of the literature finds no case of a child less than 6 years old living alone, in the wild, or on urban streets.

Two of the important physical developmental milestones of childhood are the replacement of the deciduous teeth with the eruption of the first permanent teeth and completion of brain growth in terms of weight. First molar eruption takes place, on average, between 5.5 and 6.5 years old in most human populations. Eruption of the central incisor quickly follows, or sometimes precedes, the eruption of the first molar. By the end of childhood, usually at 7 years old, most children have erupted the four first molars, and permanent incisors have begun to replace "milk" incisors. Along with growth in size and strength of the jaws and the muscles for chewing, these new teeth provide sufficient capabilities to eat a diet similar to that of adults. At this stage of development, not only is the child capable dentally of processing an adult-type diet; the nutrient requirements for brain growth also diminish. Moreover, cognitive and emotional capacities mature to new levels of self-sufficiency. Language and symbolic thinking skills mature rapidly, social interaction in play and learning become common, and the 7-year-old individual can perform many basic tasks, including food preparation, with little or no supervision.

Another feature of the childhood phase of growth associated with these physical and mental changes is the modest acceleration in growth velocity at about 6–8 years old, called the *midgrowth spurt* (shown in Figure 14-3). The midgrowth spurt is linked with an endocrine event called *adrenarche*, the progressive increase in the secretion of adrenal androgen hormones. Adrenal androgens produce the midgrowth spurt in height, a transient acceleration of bone maturation, and the appearance of axillary and pubic hair. They also seem to regulate the development of body fatness and fat distribution. The mechanism controlling adrenarche is not understood because no known hormone appears to cause it. (For complete discussions of the endocrine control of adrenarche, see Chapters 2, 4, and 5.)

Adrenarche is found only in chimpanzees and humans, and the midgrowth spurt is apparently unique to human beings. The physical changes induced by adrenarche are accompanied by a change in cognitive function, called the *5- to 7-year-old shift* by some psychologists, or the shift from the preoperational to concrete operational stage, using the terminology of Piaget. This shift leads to new learning and work capabilities in the juvenile. Adrenarche and the human midgrowth spurt may function as a life history event, marking the transition from the childhood to the juvenile growth stage.

In summary, *human childhood* is defined by the following traits:

- Slow and steady rate of growth and relatively small body size.
- A large, fast-growing brain.
- Higher RMRs than any other mammalian species.
- Immature dentition.
- Motor immaturity.
- Cognitive immaturity.
- Both adrenarche and the midgrowth spurt.

No other mammalian species has this entire suite of features.

Juvenile

The human juvenile stage begins at about 7 years old. In girls, the juvenile period ends, on average, at about 10 years old, 2 years before it usually ends in boys, the difference reflecting the earlier onset of adolescence in girls. The juvenile stage is characterized by the slowest rate of growth since birth. Studies of juvenile primates and human juveniles in many cultures indicate that much social learning takes place during this stage. Human boys and girls learn a great deal about important adult activities, including the production of food and methods of infant and child care. The completion of growth in weight of the brain and the onset of new cognitive competencies allow for this increased intensity of learning. Because juveniles are prepubertal, they can attend to this kind of social learning without the distractions caused by sexual maturation. As an aside, the start of the juvenile stage coincides with entry into traditional formal schooling in the industrialized nations. The connection is hardly a coincidence, because the juvenile stage allows for the kinds of learning and socialization found in school environments.

Adolescence

Human adolescence is the stage of life when social and sexual maturation takes place. Adolescence begins with puberty, or more technically with gonadarche, which is an event of the neuroendocrine system.[5] The current understanding of the control of gonadarche is that one, or perhaps a few, centers of the brain change their pattern of neurological activity and their influence on the hypothalamus. The hypothalamus, which has been basically inactive in terms of sexual development since about 3 years old, is again stimulated to produce GnRH. It is not known exactly how this change takes place. As stated already, the production of GnRH by the hypothalamus becomes inhibited by about 2 years old. The "inhibitor" has not been identified but likely is located in the brain and certainly not in the gonads. Human children born without gonads as well as rhesus monkeys and other primates whose gonads have been surgically removed still undergo both hypothalamus inhibition in infancy and hypothalamus reactivation at puberty. (See Chapters 4 and 5 for a detailed discussion of the hormonal control of puberty)

None of these hormonal changes can be seen without sophisticated technology, but the effects of gonadarche can be noted easily as visible and audible signs of sexual maturation. One such sign is a sudden increase in the density of pubic hair (indeed, the term *puberty* is derived from the Latin *pubescere* meaning, "to grow hairy"). In boys, the deepening of the voice is another sign of puberty. In girls, a visible sign is the development of the breast bud, the first stage of breast development. The pubescent boy or girl, his or her parents, and relatives, friends, and sometimes everyone else in the social group can observe these signs of early adolescence.

The adolescent stage also includes development of other secondary sexual characteristics, such as development of the external genitalia, sexual dimorphism in body size and composition, and the onset of greater interest and practice of adult patterns of sociosexual and economic behavior. These physical and behavioral changes occur with puberty in many species of social mammals. What makes human adolescence unusual among the primates are two important differences. The first is the length of time between age at the initiation of puberty and age at first birth. Humans take, on average, at least 10 years for this transition. The average ages for girls are the initiation of puberty at 9 and first birth at 19 years old; for boys, puberty starts at 11 and fatherhood at 21–25 years old. The reasons for delay between puberty and parenthood are discussed later. The point to make here is that monkeys and apes take less than 3 years to make the transition from puberty to parenthood.

The second human difference is that, during this life stage, both boys and girls experience a rapid acceleration in the growth velocity of almost all skeletal tissue—the adolescent growth spurt. Other primate species may show a rapid acceleration in soft tissue growth, such as muscle mass in many male monkeys and apes. However, unlike humans, other primate species either have no acceleration in skeletal growth or a very small increase in growth rate.[6] Another important ape-human difference in growth is that, by the time a chimpanzee begins its modest acceleration in long bone growth, the animal has already completed 88% of its skeletal growth. At the onset of the human adolescent growth spurt, boys and girls have completed only 81% of their skeletal growth. That 9% difference in skeletal maturation will disappear only after the human adolescent completes his or her adolescent growth spurt. Clearly, the human pattern of growth following gonadarche is quantitatively different in terms of amount, rate, and duration of growth from the pattern for other primates. The human skeletal growth spurt is unequaled by other species, and when viewed graphically, the growth spurt almost defines human adolescence (Figure 14-3). I say almost, because human adolescence is also defined by several other changes in behavior and cognition that are found only in our species. I discuss these changes in later sections.

Adolescence ends and early adulthood begins with the completion of the growth spurt, the attainment of adult stature, and the achievement of full reproductive maturity, meaning both physical and psychosocial maturity. Height growth stops when the long bones of the skeleton (e.g., femur, tibia) lose their ability to increase in length. Reproductive maturity is another hallmark of adulthood. All these developments coincide, on average, by about 19 years old in women and 21–25 years old age in men.

The course of growth and development during the prime reproductive years of adulthood is relatively uneventful. The most striking feature of the prime adult stage of life is its stability, or homeostasis, and its resistance to pathological influences, such as disease-promoting organisms and psychological stress. Old age and senescence follow the prime years of adulthood. There are many theories about the aging process and about why we must age at all. Stated simply, the inability of all cell types to use nutrients and repair damage leads to aging and death. The aging period is one of gradual or sometimes rapid decline in the ability to adapt to environmental stress. The pattern of decline varies greatly among individuals. Although specific molecular, cellular, and organismic changes can be measured and described, not all changes occur in all people, and rarely do they follow a well-established sequence. Unlike the biological self-regulation of growth prior to adulthood, the aging process appears to follow no biological or genetic plan. Menopause may be the only event of the later adult years that is experienced universally by women who live past 50 years old; men have no similar event. I discuss the biology and possible value of menopause later in this chapter.

EVOLUTION OF THE HUMAN LIFE CYCLE

Why Do New Life Stages Evolve?

In *Size and Cycle*, Bonner[7] develops the idea that the stages of the life cycle of an individual organism, colony, or society are "the basic unit of natural selection." Bonner's focus on life-cycle stages follows in the tradition of many of the nineteenth century embryologists, who proposed that speciation is often achieved by altering rates of growth of existing life stages and adding or deleting stages. Bonner shows that the presence of a stage and its duration in the life cycle relate to such basic adaptations as locomotion, reproductive rates, and food acquisition. From this theoretical perspective, it is profitable to view the evolution of human childhood, adolescence, and perhaps menopause as adaptations for both feeding and reproduction.

Why Childhood?

Consider the data shown in Figure 14-5, which depicts several hominoid developmental landmarks. Compared with living apes, human beings experience

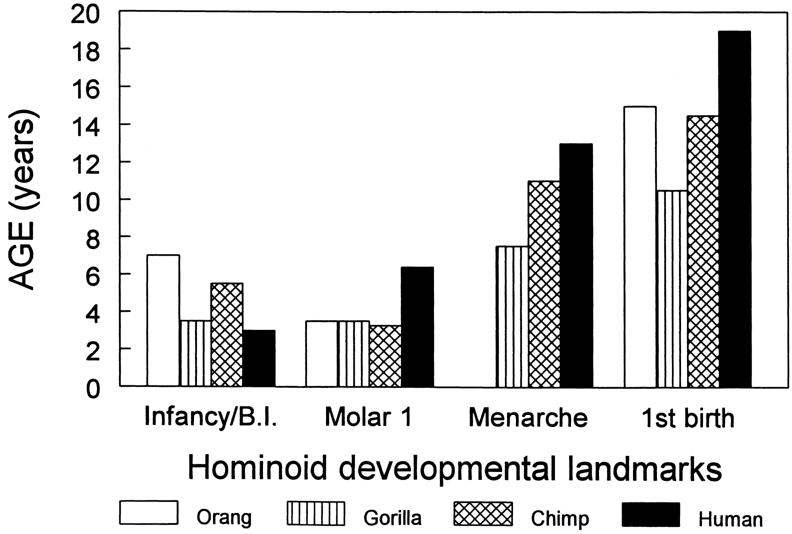

FIGURE 14-5 Hominoid developmental landmarks. Data based on observations of wild-living individuals or, for humans, healthy individuals from various cultures. Infancy/BI is the period of dependency on mother for survival, usually coincident with mean age at weaning or a new birth (where BI is birth interval); Molar 1 is mean age at eruption of first permanent molar; Menarche is mean age at first estrus or menstrual bleeding; 1st birth is mean age of females at first offspring delivery. Orang, *Pongo pygmaeus*; gorilla, *Gorilla gorilla*; chimp, *Pan troglodytes*; human, *Homo sapiens*.

developmental delays in eruption of the first permanent molar, age at menarche, and age at first birth. However, humans have a shorter infancy and a shorter birth interval, which in apes and traditional human societies almost coincide. Females of all other species of primates cannot wean their current infant until the first permanent molar (M1) erupts and their infants have learned to forage for themselves. For chimpanzees, this takes five to six years. Women in traditional societies wait, on average, 3 years between births, not the 6 years expected on the basis of M1 eruption. Human 3 years olds cannot forage for themselves and require continued care and feeding. The short birth interval gives humans a distinct advantage over other apes, because we can produce and rear two offspring through infancy in the time it takes chimpanzees or orangutans to produce and rear one offspring. By reducing the length of the infancy stage of life (i.e. lactation) and by developing the special features of the human childhood stage, humans have the potential for greater lifetime fertility than any ape.

Selection for increased reproductive success is the force that drives much of biological evolution. The evolution of the human childhood stage gave our species this reproductive advantage, because children are no longer fed by nursing. Children still depend on older individuals for feeding and protection. The child must be given foods specially chosen and prepared. But, the mother does not have to provide 100% of offspring nutrition and care directly. Indeed, traditional societies deal with the problem of childcare by spreading the responsibility among many individuals, including older juveniles, adolescents, and other adults, especially grandmothers.

In the African hunter-gatherer society of the Hadza, for example, grandmothers and greataunts supply a significant amount of food and care to children. In the Agta hunter-gatherer society of the Philippines, women hunt large game animals but still retain primary responsibility for child care. They accomplish this dual task by living in extended family groups—two or three brothers and sisters, their spouses, children, and parents—and sharing the childcare. Among the Maya of Guatemala, who are horticulturists and agriculturists, many people live together in extended family compounds. Women of all ages work together in food preparation, clothing manufacture, and childcare. In some societies, fathers provide significant childcare, including the Agta and the Aka pygmies, hunter-gatherers of central Africa. Summarizing the data from many human societies, Lancaster and Lancaster[8] call this kind of child care and feeding *the hominid adaptation* because no other primate or mammal does all this.

Childhood also may be viewed as a mechanism that allows for more precise "tracking" of ecological conditions by allowing more time for developmental plasticity. The fitness of a given phenotype (i.e., the physical features and behavior of an individual) varies across the range of variation of an environment. When phenotypes are fixed early in development, such as in mammals that mature sexually soon after weaning (e.g., rodents), environmental change and high mortality are positively correlated. The human childhood stage adds 4 years of relatively slow physical growth and allows for behavioral experience that further enhances developmental plasticity. Childhood explains, in part, the reason why a greater percentage of human young survive to adulthood than the young of any other mammalian species.

Why Adolescence?

An adolescent stage of human growth may have evolved to provide the time to practice the complex social skills required for effective parenting. The evolution of childhood afforded hominid women the opportunity to give birth at shorter intervals, but producing offspring is only a small part of reproductive fitness. Rearing the young to their own reproductive maturity is a surer indicator of success.

Studies of yellow baboons, toque macaques, and chimpanzees show that between 50 and 60% of firstborn offspring die in infancy (see Bogin[9] for references). By contrast, in hunter-gatherer human societies, between 39% (the Hadza of eastern Africa) and 44% (the !Kung of southern Africa) of offspring die in infancy. Studies of wild baboons by Altmann[10] show that, whereas the infant mortality rate for the firstborn is 50%, mortality for secondborn drops to 38%, and for third- and fourthborn reaches only 25%. The difference in infant survival is, in part, due to experience and knowledge gained by the mother with each subsequent birth.

Women internalize such maternal information during their juvenile and adolescent stages, giving these adults a reproductive advantage. The initial human advantage may seem small, but it means that up to 21 more people than baboons or chimpanzees survive out of every 100 firstborn infants—more than enough over the vast course of evolutionary time to make the evolution of human adolescence an overwhelmingly beneficial adaptation.

In human societies, juvenile girls often are expected to provide significant amounts of childcare for their younger siblings, whereas in most other social mammal groups, the juveniles are often segregated from adults and infants. Thus, human girls enter adolescence with considerable knowledge of the needs of young children. Adolescent girls gain knowledge of sexuality and reproduction because they look mature sexually, and are treated as such, several years before they actually become fertile. The adolescent growth spurt serves as a signal of maturation. Early in the spurt, before peak height velocity is reached, girls develop pubic hair and fat deposits on breasts, buttocks, and thighs. They appear to be maturing sexually. Less than a year after peak height velocity, girls experience menarche, an unambiguous external signal of internal reproductive system development. However, anovulatory menstrual cycles are relatively common in the first few years after menarche. Worthman[11] reviewed data on ovulation frequency among Swiss and Finnish girls. Ovulation frequency varied from 0 to 10% of menstrual cycles at 6 months postmenarche. The frequency increased to about 30% after 1.5 years, varied between 40 and 55% after 2.5 years, and leveled off at 60–65% after 4.5 years. Since the mature level of ovulatory frequency is about 65% of menstrual cycles, it appears that it takes about 5 years for healthy, well-nourished girls to achieve adult maturity for fertility. Nevertheless, the dramatic changes of adolescence stimulate both the girls and the adults around them to participate in adult social, sexual, and economic behavior. For the postmenarchial adolescent girl, this participation is "risk free" in terms of pregnancy for 1 or more years.

It is noteworthy that female chimpanzees and bonobos, like human girls, also experience up to 3 years of postmenarchial infertility, so this time of life may be a shared hominoid trait. Like human adolescents, the postmenarchial but infertile chimpanzees and bonobos participate in a great deal of adult social and sexual behavior. Primate researchers observing these apes point out that this participation, without pregnancy, allows for practicing many key behaviors needed to successfully rear an infant.

Although ape and human females may share a year or more of adolescent sterility, apes reach adulthood sooner than humans. Full reproductive maturation in human women is not achieved until about 5 years after menarche. The average age at menarche in the United States is 12.4 years, which means that the average age at full sexual maturation occurs between 17 and 18 years old. Although adolescents younger than these ages can have babies, both the teenage mothers and the infants are at risk because of the reproductive immaturity of the mother. Risks include a low-birth-weight infant, premature birth, and high blood pressure in the mother.

The likelihood of these risks declines and the chance of successful pregnancy and birth increases markedly after 18 years old.

Another feature of human growth not found in the African apes is that female fertility tracks the growth of the pelvis. Ellison[12] and Worthman[11] found that age at menarche is best predicted by biiliac width, the distance between the iliac crests of the pelvis. A median width of 24 cm is associated with average menarcheal age in samples of American girls living in Berkeley, California; Kikuyu girls of East Africa; and Bundi girls of highland New Guinea. The median pelvic width of 24 cm occurs at different ages in these three cultures, about 13, 16, and 17 years old, respectively. The later ages for menarche are due to chronic malnutrition and disease in Kenya and Bundi. This association does not mean that a pelvic width of 24 cm is critical or indeed necessary for menarche to occur. A median value of 24 cm means that 50% of girls will have pelvic breadths less than 24 cm and 50% greater than 24 cm at menarche.

Moerman[13] also reported a special human relationship between growth in pelvic size and reproductive maturation. She found that the crucial variable for successful first birth is size of the pelvic inlet, the bony opening of the birth canal. Moerman measured pelvic X rays from a sample of healthy, well-nourished American girls who achieved menarche between 12 and 13 years old. These girls did not attain adult pelvic inlet size until 17–18 years old. Quite unexpectedly, the adolescent growth spurt, which occurs before menarche, does not influence the size of the pelvis in the same way as the rest of the skeleton. Rather, the female pelvis has its own slow pattern of growth, which continues for several years after adult stature is achieved.

Cross-cultural studies of reproductive behavior show that human societies acknowledge (consciously or not) this special pattern of pelvic growth. The age at marriage and first childbirth clusters around 19 years for women from such diverse cultures as the Kikuyu of Kenya, Mayans of Guatemala, Copper Eskimos of Canada, and both the colonial and contemporary United States. Why the pelvis follows this unusual pattern of growth is not clearly understood. Perhaps another human attribute, bipedal walking, is a factor. Bipedalism is known to have changed the shape of the human pelvis from the basic apelike shape. Apes have a cylindrical-shaped pelvis, but humans have a bowl-shaped pelvis. The human shape is more efficient for bipedal locomotion but less efficient for reproduction because it restricts the size of the birth canal. Whatever the cause, this special human pattern of pelvic growth helps explain the delay from menarche to full reproductive maturity. That time of waiting provides the adolescent girls many opportunities to practice and learn important adult behaviors that lead to increased reproductive fitness in later life.

WHY DO BOYS HAVE ADOLESCENCE?

The adolescent development of boys is quite different from that of girls. Boys become fertile well before they assume the size and the physical characteristics of men. Analysis of urine samples from boys 11–16 years old show that they begin producing sperm at a median age of 13.4 years. Yet cross-cultural evidence indicates that few boys successfully father children until they are into their third decade of life. In the United States, for example, only 3.09% of live-born infants in 1990 were fathered by men under 20 years of age. Among the traditional Kikuyu of East Africa, men do not marry and become fathers until about age 25 years, although they become sexually active after their circumcision rite at around age 18.

The explanation for the lag between sperm production and fatherhood is not likely to be a simple one of sperm performance, such as not having the endurance to swim to an egg cell in the woman's Fallopian tubes. More likely is the fact that the average boy of 13.4 years is only beginning his adolescent growth spurt (Figure 14-3). Growth researchers have documented that in terms of physical appearance, physiological status, psychosocial development, and economic productivity, the 13-year-old boy is still more of a juvenile than an adult. Anthropologists working in many diverse cultural settings report that few women (and more important from a cross-cultural perspective, few prospective in-laws) view the teenage boy as a biologically, economically, and socially viable husband and father.

The delay between sperm production and reproductive maturity is not wasted time in either a biological or social sense. The obvious and the subtle psychophysiological effects of testosterone and other androgen hormones released after gonadal maturation may "prime" boys to be receptive to their future roles as men. Alternatively, it is possible that physical changes provoked by the endocrines provide a social stimulus toward adult behaviors. Whatever the case, early in adolescence, sociosexual feelings, including guilt, anxiety, pleasure, and pride, intensify. At the same time, adolescent boys become more interested in adult activities, adjust their attitude to parental figures, and think and act more independently. In short, they begin to behave like men.

However—and this is where the survival advantage may lie—they still look like boys. One might say that a healthy, well-nourished 13.5-year-old human male, at a median height of 160 cm (62 in.) "pretends" to be more childlike than he really is. Because their adolescent growth spurt occurs late in sexual development, young males can practice behaving like adults before they are actually perceived as adults. The sociosexual antics of young adolescent boys are often considered to be more humorous than serious. Yet, they provide the experience to fine-tune their sexual and social roles before their lives or those of their offspring depend on them. For example, competition among men for women favors the older, more experienced man. Because such competition may be fatal, the childlike appearance of the immature but hormonally and socially primed adolescent male may be life-saving as well as educational.

WHEN DID CHILDHOOD AND ADOLESCENCE EVOLVE?

The stages of the life cycle may be studied directly only for living species. However, we can postulate on the life cycle of extinct species. Such inferences for the hominids are, of course, hypotheses based on comparative anatomy, comparative physiology, comparative ethology, and archeology. Examples of such methods are found in the work of Martin[14] and Harvey, Martin, and Cluton-Brock[15] on patterns of brain and body growth in apes, humans, and their ancestors.

Apes have a pattern of brain growth that is rapid before birth and relatively slower after birth. In contrast, humans have rapid brain growth both before and after birth (Figure 14-6). This difference may be illustrated by comparing ratios of brain weight divided by total body weight, the data are given in Table 14-2. At birth, this ratio averages 0.09 for the great apes and 0.12 for humans, showing that, in proportion to body size, humans are born with brains that average 1.33 times larger than those of the apes. At adulthood, the ratio averages 0.008 for the great apes and 0.028 for humans, meaning that the difference between apes and humans in the brain-to-body size proportion has increased to 3.5 times. The faster rate of human brain growth after birth accounts for most of the difference. Indeed, the rate of human brain growth exceeds that of most other tissues of the body during the first few years after birth (Figure 14-4).

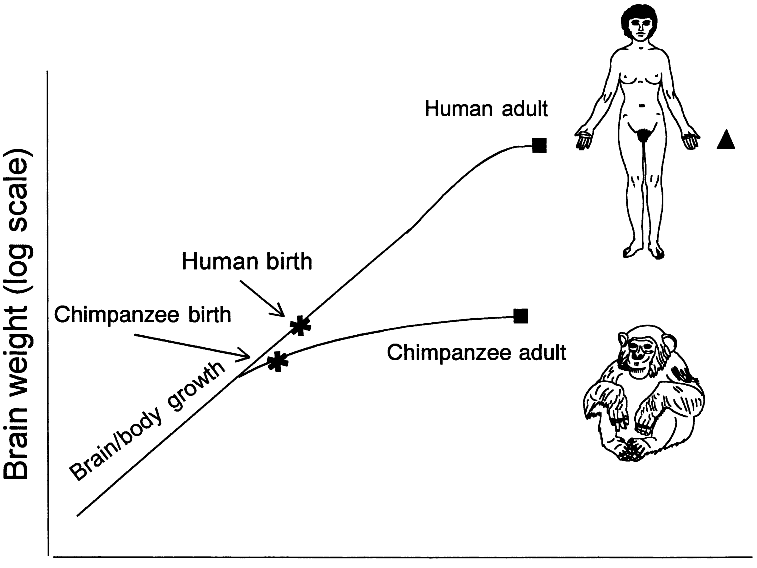

FIGURE 14-6 Brain and body growth curve for humans compared with chimpanzees. The length of the human fetal phase, in which brain and body grow at the same rate for both species, is extended for humans. In chimpanzees, brain growth slows after birth, but in humans, the high rate of brain growth is maintained during the postnatal phase. In contrast, the rate of human body growth slows after birth. If human brain and body growth rates were equal to those of chimpanzees, then adult humans would weigh 454 kg (998.8 lb) and stand nearly 3.1 m tall (9.9 ft), that body size is indicated by the ▲ symbol.

TABLE 14-2 Neonatal and Adult Brain Weight and Total Body Weight for the Great Apes and Human Beings

	Neonatal Weight (grams)		Adult Weight (grams)	
Species	Brain	Body	Brain	Body
Pongo (orangutan)	170.3	1728.0	413.3	5300
Pan (chimpanzee)	128.0	1756.0	410.3	3635
Gorilla	227.0	2110.0	505.9	12,650
Homo sapiens	384.0	3300.0	1250.0	4400

Adult body weight is the average of male and female weight.

Source: Data from Harvey, Martin, and Cluton-Brock.[15]

Martin's analysis of ape and human trajectories of growth indicate that a "human-like" pattern of brain and body growth becomes necessary after adult hominid brain size reaches ±850 cubic centimeters (cc). This biological marker is based on an analysis of the size of the head of the fetus and the size of the pelvic inlet (birth canal) of the mother across a wide range of social mammals, including the living primates and fossil hominids. Given the mean rate of postnatal brain growth for living apes, an 850-cc adult brain size may be achieved by all hominoids, including extinct hominids, by lengthening the fetal stage of growth. At brain sizes greater than 850 cc, the size of the pelvic inlet of the fossil hominids and living humans does not allow for sufficient fetal growth. Therefore, a period of rapid postnatal brain growth and slow body growth—the human pattern—is needed to reach adult brain size.

From this analysis, we can see clearly why so much of human postnatal growth and development is intimately associated with brain size. I presented earlier the figures on the percent of RMR due to brain growth and activity. The relation of human life history to our large and active brain can be looked at as an energetic problem. Large brains are costly investments; recall that the adult human brain uses 20% of RMR, whereas the chimpanzee uses only 9% and an average marsupial only 2%. Moreover, larger brains have lower tolerances for temperature extremes, blood pressure, and oxygenation. The large human brain may increase obstetric risks (birth defects and maternal death). The costs are potentially high, but what is the payoff? The explanation I favor here is that a large brain is an investment that pays off on a long time scale. An organism recoups its energetic "investment" in a large brain through complex behavior, which is itself a combined product of large brains, slow development, extended care by older individuals, enhanced learning, and phenotypic plasticity, among other influences. The benefits of large brains probably accrue slowly over a long life. For primates in general and humans in particular, much of life history may support a substantial investment in brains.

We are, perhaps, fortunate that brains are so important, because after teeth and jaws, skulls are one of the more common pieces of fossil evidence preserved in the record of primate evolution. Having skulls, or at least sufficient skull parts to reconstruct the whole, allows paleontologists to estimate brain size. Having teeth and jaws in relative abundance is also fortuitous because of the strong correlation between tooth formation and eruption and so many life history events.

Given this background, Figure 14-7 is an attempt to summarize the evolution of the human pattern of growth and development. This figure must be considered as "a work in progress," because only the data for *Pan* and *Homo sapiens* are known with some certainty. Known ages for eruption of the M1 are given for *Pan* and *H. sapiens*. Smith and Tompkins[16] calculated estimated ages for M1 eruption in other species. Age of eruption of M1 is an important life history event that correlates very highly with other life history events. Known or estimated adult brain sizes are given at the top of each bar; the estimates are averages based on reports in several textbooks of human evolution. Brain size is another crucial influence on life history evolution. (Further details and references for this and the following discussion of Figure 14-7 may be found in Bogin[9]).

Australopithecus afarensis appears in the fossil record about 3.9 million years ago (MYA) and is one of the oldest hominid fossil species. *A. afarensis* shares many anatomical features with nonhominid pongid (ape) species, including an adult brain

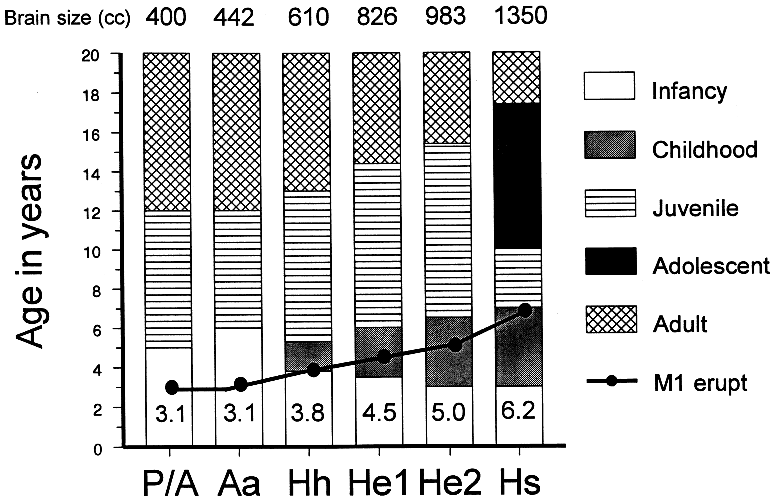

FIGURE 14-7 The evolution of hominid life history during the first 20 years of life. Abbreviated nomenclature as follows: P/A, *Pan* and *Australopithecus afarensis*; Aa, *Australopithecus africanus*; Hh, *Homo habilis*; He1, early *Homo erectus*; He2, late *Homo erectus*; Hs, *Homo sapiens*. Mean brain sizes are given at the top of each histogram. Mean age at eruption of the first permanent molar (M1) is graphed across the histograms and given below the graph.

size of about 400 cc and a pattern of dental development indistinguishable from extant apes. Therefore, the chimpanzee and *A. afarensis* are depicted as sharing the typical tripartite stages of postnatal growth of social mammals: infant, juvenile, adult. The duration of each stage and the age at which each stage ends are based on empirical data for the chimpanzee. A probable descendent of *A. afarensis* is the fossil species *A. africanus*, dating from about 3.0 MYA. To achieve the larger adult brain size of *A. africanus* (average of 442 cc) may have required an addition to the length of the fetal or infancy period or both. Figure 14-7 indicates an extension to infancy of 1 year.

About 2.2 MYA fossils with several more humanlike traits, including larger cranial capacities and greater manual dexterity, appear. Also dated to about this time are stone tools of the Oldowan tradition. Given the biological and cultural developments associated with these fossils, they are considered by most paleontologists to be members of the genus *Homo* (designated as *H. habilis, H. rudolfensis*, or early *H. erectus*—referred to collectively here as *H. habilis)*. The rapid expansion of adult brain size during the time of *H. habilis* (650–800 cc) might have been achieved with further expansion of both the fetal and infancy periods, as Martin's "cerebral Rubicon" was not surpassed. However, the insertion of a brief childhood stage into hominid life history may have occurred. Tardieu[17] showed that *H. habilis* has a pattern of growth of the femur that is distinct from that of the australopithecines but consistent with that of later hominids. The distinctive femur shape of the more recent hominids is due to the addition of a prolonged childhood stage of growth. *H. habilis*, then, may have had a short childhood stage of growth.

This stage begins after the eruption of M1 and lasts for about 1 year. That year of childhood would still provide the time needed to learn about finding and processing adult-type foods. During this learning phase, *H. habilis* children would need to be supplied with special weaning foods. There is archaeological evidence for just such a scenario. *H. habilis* seems to have intensified its dependence on stone tools. More stone tools, more carefully manufactured tools, and a greater diversity of stone tool types are associated with *H. habilis*. There is considerable evidence that some of these tools were used to scavenge animal carcasses, especially to break open long bones and extract bone marrow. This behavior may be interpreted as a strategy to feed children. Such scavenging may have been needed to provide the essential amino acids, some of the minerals, and especially the fat (dense source of energy) that children require for growth of the brain and body.

Further brain size increase occurred during *H. erectus* times, which begin about 1.6 MYA. The earliest adult specimens have mean brain sizes of 826 cc, but many individual adults had brain sizes between 850 and 900 cc. This places *H. erectus* at or above Martin's "cerebral Rubicon" and seems to justify insertion or expansion of the childhood period to provide the biological time needed for the rapid, humanlike pattern of brain growth. Note from Figure 14-7 that the model of human evolution proposed here predicts that, from the *Australopithecus* to the *H. erectus* stage, the infancy period shrinks as the childhood stage expands. Perhaps, by early *H. erectus* times, the transition from infancy to childhood took place before

M1 eruption. Of course, it is not possible to know if this was the case or to state the cause of such a life history change with any certainty. Maybe the evolution of ever-larger brains led to a delay in M1 eruption, which in turn led to both the need for a childhood stage and the expansion of the childhood stage, as brains continued to enlarge. Alternatively, a delay in dental maturation may have precipitated the need for childhood and in turn the biocultural ecology of childhood and its effects on hominid social learning and behavior selected for ever larger brains. No matter what the cause of childhood may be, if an expansion of childhood led to a shrinking of the infancy stage, then *H. erectus* would have enjoyed a greater reproductive advantage than any previous hominid. This seems to the case, as *H. erectus* populations certainly increased in size and began to spread throughout Africa and into other regions of the world.

Later *H. erectus*, with average adult brain sizes of 983 cc, are depicted with further expansion of the childhood stage. In addition to bigger brains (some individuals had brains as large as 1100 cc), the archaeological record for later *H. erectus* shows increased complexity of technology (tools, fire, and shelter) and social organization. These technosocial advances, and the increased reliance on learning that occur with these advances, may well be correlates of changes in biology and behavior associated with further development of the childhood stage of life[18] The evolutionary transition to archaic, and finally modern, *H. sapiens* expands the childhood stage to its current dimension. Note that M1 eruption becomes one of the events that coincide with the end of childhood. Perhaps no further extension of childhood beyond M1 eruption is possible, given the significant biological, cognitive, behavioral, and social changes linked with dental maturation and the end of childhood. With the appearance of *H. sapiens* comes evidence for the full gamut of human cultural capacities and behaviors. The technological, social, and ideological requisites of culture necessitate a more intensive investment in learning than at any other grade of hominid evolution. The learning hypothesis for childhood, while not sufficient to account for its origins, certainly plays a significant role in the later stages of its evolution.

The *H. sapiens* grade of evolution also sees the addition of an adolescent stage to postnatal development. The single most important feature defining human adolescence is the skeletal growth spurt experienced by virtually all boys and girls. There is no evidence for a humanlike adolescent growth spurt in any living ape. There is no evidence for adolescence for any species of *Australopithecus*. There is some tentative evidence that early *Homo*, dating from 1.8 MYA, may have a derived pattern of growth leading toward the addition of an adolescent stage of development. This evidence is based on an analysis of shape change during growth of the femur.[17] Modern humans have highly diagnostic shape to the femur, a shape absent in fossils ascribed to *Australopithecus* but present in fossils ascribed to *Homo habilis*, *Homo rudolfensis*, and early African *Homo erectus*. The human shape is produced by growth changes during both the prolonged childhood stage and the adolescent stage. The more humanlike femur shape of the early *Homo* fossils could be due to the insertion of the childhood stage alone or to the combination of childhood and adolescent stages. Due to the lack of fossils of appropriate age at death, the lack of dental and skeletal material from the same individuals, and the lack of sufficient skeletal material from other parts of the body, it is not possible to draw any more definitive conclusions.

A remarkable fossil of early *Homo erectus* is both of the right age at death and complete enough to allow for an analysis of possible adolescent growth. The fossil specimen is catalogued formally by the name KMN-WT 15000, but is called informally the *Turkana boy*, as it was discovered along the western shores of Lake Turkana in 1984. This fossil is 1.6 million years old, making it an early variety of *Homo erectus*. The skeletal remains are almost complete, missing the hands and feet and a few other minor bones. Smith[19] analyzed the skeleton and dentition of the Turkana fossil and ascertained that, indeed, it is most likely the remains of an immature male. The youth's deciduous upper canines were still in place at the time of death, and he died not long after erupting second permanent molars. These dental features place him firmly in the juvenile stage by comparison with any hominoid. The boy was 160 cm tall at the time of death, which makes him one of the tallest fossil youths or adults ever found.

Part of Smith's analysis focused on patterns of growth and development, especially the question, Did early *H. erectus* have an adolescent growth spurt? Based on her analysis, the answer to that question is, No. Judged according to modern human standards, the Turkana boy's dental age of 11 years is in some conflict with his bone age (skeletal maturation) of 13 years and his stature age of 15 years. If the Turkana boy grew along a modern human trajectory, then dental, skeletal and stature ages should be about equivalent. By chimpanzee growth standards, however, the boy's dental and bone ages are in perfect agreement, both at 7 years old. As *Homo erectus* is no chimpanzee, the Turkana boy's true age at death was probably between 7 and 11 years old. What is clear is that the Turkana boy followed a pattern of growth that is neither that of a modern human nor that of a chimpanzee. Based on Smith's analysis, the boy's large stature becomes more explicable. The reason for his relatively large stature for age is that the distinct human pattern of moderate to slow growth prior to puberty followed by an adolescent growth spurt had not yet evolved in early *Homo erectus*. Rather, the Turkana boy followed a more apelike pattern of growth in stature, making him appear to be tall in comparison with a modern human boy at the same age. At the time of puberty, the chimpanzee has usually achieved 88% of stature growth, while humans have achieved only 81%. Smith and Tompkins[16] state that the human pattern of growth suppression up to puberty followed by a growth spurt after puberty had not evolved by early *H. erectus* times. "Because of this, any early *H. erectus* youth would seem to us to be too large"(p. 273).

Unfortunately, no appropriate fossil materials of later *H. erectus* are available to analyze for an adolescent growth spurt. Several fossils of a species called *Homo antecessor* were found in Spain.[20] This species is also called *early H. sapiens* by many paleontologists. These fossils date from about 800,000 BP (before present).

Based on an analysis of tooth formation, this species seems to have a pattern of dental maturation equal to that of living people. Perhaps, the species had a pattern of skeletal growth, including an adolescent growth spurt, like that of living people as well.

One possible descendant of so-called *Homo antecessor* is the Neandertals. There is one fossil of a Neandertal in which the associated dental and skeletal remains needed to assess adolescent growth are preserved. The specimen is a juvenile, most likely a male. It is called Le Moustier 1 and was found in 1908 in Western France. The specimen is dated at between 42,000 and 37,000 years BP. Thompson and Nelson[21] estimated that this youth has a dental age of 15.5 ±1.25 years and a stature age of about 11 years, based on the length of his femur. The dental age and the stature age are in very poor agreement and indicate that, like the Turkana boy, Le Moustier 1 may not have followed a human pattern of adolescent growth. Quite unexpectedly, these differences in dental and skeletal maturity are exactly the opposite of those for the Turkana boy.

What is clear is that the adolescent growth stage, and the adolescent growth spurt, evolved only in the *Homo sapiens* line. Quite likely, this would be no earlier than the appearance of archaic *H. sapiens* in Africa about 125,000 years ago or in *H. antesesor* 800,000 years ago. If Neandertals are direct ancestors to modern humans, as some scientists believe, then the adolescent skeletal growth spurt may be less than 37,000 years old.

THE VALUABLE GRANDMOTHER, OR COULD MENOPAUSE EVOLVE?

In addition to childhood and adolescence, human life history has another unusual aspect: menopause. One generally accepted definition of menopause is "the sudden or gradual cessation of the menstrual cycle subsequent to the loss of ovarian function."[22] The process of menopause is closely associated with but distinct from the adult female postreproductive stage of life. Reproduction usually ends before menopause. In traditional societies, such as the !Kung, the Dogon of Mali, and the rural-living Maya of Guatemala, women rarely give birth after age 40 and almost never give birth after age 44. Even in the United States from 1960 to 1990, with modern health care, good nutrition, and low levels of hard physical labor, women rarely gave birth after age 45. This is true even among social groups attempting to maximize lifetime fertility, such as the Old Order Amish.

As among the !Kung, Dogon, and Maya, menopause occurs well after this fertility decline, at a mean age of 49 years for living women in the United States. After age 50, births are so rare that they are not reported in the data of the U.S. National Center for Health Statistics or by the Amish. (However, they are sensationalized in the tabloids sold at supermarket checkouts.) I report these ages for the onset of human female postreproductive life versus the ages for menopause because some scholars incorrectly equate menopause with the beginning of the postreproductive stage, so one must read the literature carefully to interpret in what sense the term *menopause* is used.

Menopause, and a significant period of life after menopause, appears to be a uniquely human female characteristic. Wild-living nonhuman primate females do not share the universality of human menopause, and human males have no comparable life history event. In a review of the data for all mammals, Austad[23] finds that no wild-living species, except possibly pilot whales, "are known to commonly exhibit reproductive cessation." Female primates studied in captivity, including langurs, baboons, rhesus macaques, pigtailed macaques, and chimpanzees, usually continue estrus cycling until death, although fertility declines with age. These declines are best interpreted as a normal part of aging. Only one captive bonobo more than 40 years old and one captive pigtail macaque older than 20 are known to have ceased estrus cycling. In contrast to the senescent decline in fertility of other female primates, the human female reproductive system is abruptly "shut down" well before other systems of the body, which usually experience a gradual decline toward senescence.

There are many hypotheses for the evolution of menopause and a postreproductive life stage. There is insufficient space to review them (see Bogin[9] for a partial review). In terms of basic biology, it appears that a 50-year age barrier exists to female mammalian fertility because by that age, all oocytes are depleted. By that age, the females of most mammalian species are dead. The few exceptions are elephants and whales, the largest mammalian species, and humans. Much ethnographic evidence shows that significant numbers of women in almost every human society, traditional and industrial, live for many years after oocyte depletion (menopause). The only reproductive strategy open to postmenopausal females is to provide increasing amounts of aid to their offspring and their grandoffspring. Elephants do this, because the leader of the social group is usually an old matriarch. Little is known about the social lives of whales in terms of grandmother behavior. The ethnographic evidence shows that human grandmothers and other postreproductive women are beneficial to the survival of children in many human societies. Grandmothers provide food, childcare, and a repertoire of knowledge and life experiences that assist in the education of their grandchildren. In sum, the inevitabilities of mammalian biology, combined with the creativity of human culture, allow women (and men?) of our species to develop biocultural strategies to take greatest advantage of a postreproductive life stage. Viewed in this context, human grandmotherhood may be added to human childhood and adolescence as distinctive stages of the human life cycle.

REFERENCES

1. Halder G, Callaerts, P, Gehring WJ. New perspectives on eye evolution. Curr Opin Genet Develop. 1995;5:602–609.

2. Perieira ME, Altmann J. Development of social behavior in free-living nonhuman primates. In: Watts ES (ed). Nonhuman Primate Models for Human Growth and Development. New York: Alan R. Liss, 1985:217–309.
3. Janson CH, Van Schaik CP. Ecological risk aversion in juvenile primates: slow and steady wins the race. In: Perieira ME, Fairbanks LA (eds). Juvenile Primates: Life History, Development, and Behavior. New York: Oxford University Press, 1993:57–74.
4. Alexander RD. How Did Humans Evolve? Reflections on the Uniquely Unique Species. Special Publication No. 1. Ann Arbor: University of Michigan Museum of Zoology, 1990.
5. Weirman ME, Crowley WF, Jr. Neuroendocrine control of the onset of puberty. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 2, 2nd ed. New York: Plenum, 1986:225–241.
6. Bogin B. Evolutionary perspective on human growth. Ann Rev Anthropol. 1999;28;109–153.
7. Bonner JT. Size and Cycle. Princeton, NJ: Princeton University Press, 1965.
8. Lancaster JB, Lancaster CS. Parental investment: the hominid adaptation. In: Ortner DJ (ed). How Humans Adapt. Washington, DC: Smithsonian Institution Press, 1983:33–65.
9. Bogin B. Patterns of Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1999.
10. Altmann J. Baboon Mothers and Infants. Cambridge, MA: Harvard University Press, 1980.
11. Worthman CM. Biocultural interactions in human development. In: Perieira ME, Fairbanks LA (eds). Juvenile Primates: Life History, Development, and Behavior. New York: Oxford University Press, 1993:339–357.
12. Ellison PT. Skeletal growth, fatness, and menarcheal age: A comparison of two hypotheses. Hum Biol. 1982;54:269–281.
13. Moerman ML. Growth of the birth canal in adolescent girls. Amer J Obstet Gynecol. 1982;143:528–532.
14. Martin RD. Human Brain Evolution in an Ecological Context, Fifty-Second James Arthur Lecture. New York: American Museum of Natural History, 1983.
15. Harvey P, Martin RD, Cluton-Brock TH. Life histories in comparative perspective. In: Smuts B, Cheney DL, Seyfarth RM, Wrangham RW, Struhsaker TT (eds). Primate Societies. Chicago: University of Chicago Press, 1987:181–196.
16. Smith BH, Tompkins RL. Toward a life history of the hominidae. Ann Rev Anthropol. 1995;25:257–279.
17. Tardieu C. Short adolescence in early hominids: Infantile and adolescent growth of the human femur. Amer J Phys Anthropol. 1998;197:163–178.
18. Bogin B, Smith BH. Evolution of the human life cycle. Am J Hum Biol. 1996;8:703–716.
19. Smith BH. Physiological age of KMN-WT 15000 and its significance for growth and development of early *Homo*. In: Walker AC, Leakey RF (eds). The Nariokotome *Homo erectus* Skeleton. Cambridge, MA: Belknap Press, 1993:195–220.
20. Castro de Bermudez JM, Rosas A, Carbonell E, Nicolas ME, Rodroguez, J, Arsuaga JL. A modern human pattern of dental development in Lower Pleistocene hominids from Atapuerca-TD6 (Spain). Proc Natl Acad Sci. 1999;96:4210–4213.
21. Thompson JL, Nelson AJ. Relative postcranial development of Neandertals. J Hum Evol. 1997;32:A23–A24.
22. Timiras PS. Developmental Physiology and Aging. New York: Macmillan, 1972.
23. Austad SN. Menopause: An evolutionary perspective. Exp Gerontol. 1994;29:255–263.
24. Tanner JM. Growth and Adolesence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.
25. Coelho AM. Baboon dimorphism: growth in weight, length, and adiposity from birth to 8 years of age. In: Watts ES (ed). Nonhuman Primate Models for Human Growth. New York: Alan R. Liss, 1985.
26. Prader A. Biomedical and endocrinological aspects of normal growth and development. In: Borms J, Hauspie RR, Sand A, Susanne C, Hebbelinck M (eds). Human Growth and Development. New York: Plenum, 1984:1–22.
27. Bock RD, Thissen D. Statistical problems of fitting individual growth curves. In: Johnston FE, Roche AF, Susanne C (eds). Human Physical Growth and Maturation, Methodologies and Factors. New York: Plenum, 1980:265–290.

28. Cabana T, Jolicoeur P, Michaud J. Prenatal and postnatal growth and allometry of stature, head circumference, and brain weight in Québec children. Amer J Hum Biol. 1993;5:93–99.
29. Demirjian A. Dentition. In: Falkner F, Tanner JM (eds). Human Growth, Vol. 2. Postnatal Growth. New York: Plenum, 1986:269–298.
30. Scammon RE. The measurement of the body in childhood. In: Harris JA, et al. (eds). The Measurement of Man. Minneapolis: University of Minnesota Press, 1930:173–215.

15

EXERCISE AND GROWTH: PHYSICAL ACTIVITY AS A FACTOR IN GROWTH AND MATURATION

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INTRODUCTION

Growth and maturation are maintained primarily by the interactions of genes, hormones, energy, and nutrients. There are also environmental sources of variation. Genes, hormones, energy, and nutrients interact among themselves and also with the environments in which the individual lives. Physical activity is an environmental factor often viewed as exerting a favorable influence on growth and maturation. This chapter focuses on physical activity as a factor that may affect growth and maturation, but it is essential to recognize that physical activity is only one of many factors that may affect these processes.

Regular physical activity is often viewed as essential to normal growth and maturation. Studies spanning nearly a century have suggested that regular physical activity has a stimulatory influence on growth and maturation. In one of the first comprehensive reviews of "exercise and growth," Rarick[1] suggested:

> *certain minima of muscular activity are essential for supporting normal growth and for maintaining the protoplasmic integrity of the tissues. What these minima mean in terms of intensity and duration of activity has not been ascertained. (p. 459)*

At the same time, concern has also been expressed about potentially negative influences of physical activity, specifically of intensive training for sport during childhood and adolescence. Training for sport is more complex than habitual physical activity and is not considered in this chapter. The issue of intensive training for sport has been critically addressed in more detail elsewhere (Malina[2]). For the present, it is important to note that regular physical activity is not equivalent to intensive training for sport. This chapter considers habitual physical activity as a factor that may influence the growth and maturation of children and adolescents. Are the physical and physiological demands of habitual physical activity during childhood and adolescence capable of altering individual patterns of growth and maturation?

PHYSICAL ACTIVITY

Physical activity refers to gross bodily movements associated with significant increases in energy expenditure above resting levels. In addition to the energetic component (metabolic equivalents [METs], oxygen consumption), physical activity involves at least four other major components:

1. Biomechanical (weight bearing activities, ground reaction forces).
2. Strength (resistance, static, dynamic).
3. Motor skill (economy, accuracy of movements).
4. Context (the setting of activity, which is variable and culturally specific).

The energetic component of activity focuses on the balance between energy intake and energy output, the role of habitual activity in the development and maintenance of aerobic capacities (aerobic fitness), and the energy and fitness needed to carry out daily activities. The biomechanical component emphasizes the effects of the forces generated by physical activities on connective tissues and joints, and especially the mineralization of bone tissue. The strength component deals with movement against a resistance and ordinarily deals with the amount of activity needed to maintain muscular strength and power, specifically the strength needed to carry out daily activities. The motor component emphasizes proficiency in motor skills. Movement is the substrate of physical activity, and proficiency in motor skills facilitates a range of activities; conversely, lack of proficiency constrains opportunities for physical activity. The context of activity is the setting, broadly defined, within which physical activities are performed. The context is determined by the culture within which the individual lives and includes such things as what activities are acceptable, when they can be performed, values attached to activities, and so on.

Most discussions of physical activity refer to a child's estimated level of habitual physical activity; that is, the level of physical activity that characterizes the lifestyle of the individual. It is usually quantified in terms of amount of time in activity (hr/day or hr/wk), an activity score, or time or energy expended in moderate-to-vigorous activities. Estimates are ordinarily derived from questionnaires, interviews, diaries and heart rate integrators, or a combination of methods.

There is a need to qualify and quantify physical activity programs for children and adolescents, if the effects of physical activity on growth and maturation are to be identified and partitioned from other factors known to affect these outcomes. This requires more specific details about number of sessions per week, duration of activity sessions or distance covered in a session, intensity of the activity or energy cost, and type of activity, such as sprint, speed, endurance, or strength or some combination thereof.

APPROACHES TO THE STUDY OF THE EFFECTS OF PHYSICAL ACTIVITY

Three approaches have been used to evaluate the potential influence of physical activity on growth and maturation.

Comparative

The first approach compares the characteristics of children and adolescents who are habitually physically active to those who are not active. Criteria for habitual activity and inactivity vary among studies. Inactive youth in some studies, for example, participate in regular physical education and other normal daily activities of children and adolescents. Thus, they are not really inactive; they are inactive relative to youth who engage in physical activities on a more regular basis. As an example, samples of Belgian boys classified as active and nonactive were followed longitudinally from 13–18 years old. The former participated in physical activities (largely sport activities, but they were not athletes) for more than 5 hours per week per year for 3 years; the latter participated in no more than 1.5 hours per week per year for 3 years. However, depending on the school system in which the boys were enrolled, compulsory physical education varied between 1 and 3 hours per week (Beunen et al.[3]).

Comparisons of athletes and nonathletes during childhood and adolescence are occasionally used to make inferences about the influence of physical activity. It is assumed that the athletes have been training regularly, and differences relative to nonathletes are attributed to the physical activity involved in the training program. The problem with this approach is subject selectivity. Successful young athletes, especially more elite athletes, are different from nonathletes, quite often in size and maturity status (see Malina[2,4] for summaries). In addition, some sports (e.g., gymnastics, figure skating) have fairly rigid selection criteria. Hence, it is not correct to generalize from athletes to the general population of children and adolescents.

Experimental

The second approach is experimental. It involves comparison of individuals exposed to a specific physical activity program (treatment group) and those not exposed to the activity program (control group). The physical activity stimulus varies among studies in type, intensity, and duration; and subjects often vary in age at time of initiation of the program. Problems are encountered in defining and quantifying the physical activity stimulus within and across studies. Selection of subjects, variation in growth and maturity status among subjects, motivation to be active, regularity of the activity program, control of outside activity, and other factors make comparison of experimental studies difficult.

Correlational

The third approach is correlational. It considers the relationship between an estimate of habitual physical activity and an indicator of growth and maturation, such as the correlation with level of physical activity and subcutaneous fatness.

In studies of physical activity in children and adolescents, the physical activity stimulus is rarely monitored over several years. Most experimental programs are specific and short term, say, 15 or 20 weeks of endurance training in running or swimming or 8 or 12 weeks of resistance training. Rarely is a specific activity program monitored over several years. Occasionally, a systematic program of sport skill practice is the physical activity stimulus. Nevertheless, physical activity is not the same as regular training for sport. Physical activity is integral to training for sport, but training for sport refers to systematic, specialized practice for a specific sport or sport discipline for most of the year and usually over several years.

Occasionally, extreme unilateral activity involving specialized use of the arm is used to illustrate the effects of physical activity on limb muscle, skeletal, and adipose tissues. The individual is his or her own control, as the dominant limb (experimental or active limb) is compared to the nondominant limb (control or less active limb). Presently available studies of extreme unilateral activity tend to focus on athletes in racket sports such as tennis and squash, and these studies are beyond the scope of this chapter.

ACTIVITY AND STATURE

Regular physical activity has no apparent effect on attained height and rate of growth in height. Longitudinal data on active and inactive boys followed from childhood through adolescence and girls followed during childhood are shown in Figure 15-1. The means indicate either no differences or only small differences in height between the active and inactive during childhood and adolescence and in young adulthood. The issue of subject selection, probably self-selection, in the active and inactive groups is a factor to consider in making comparisons.

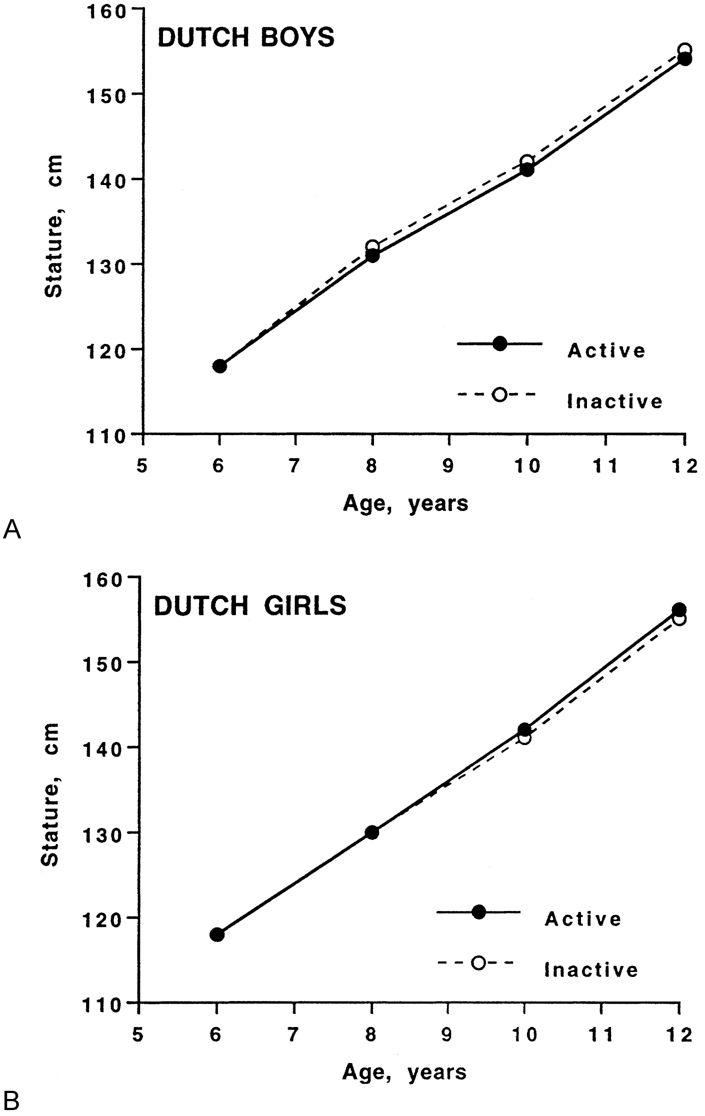
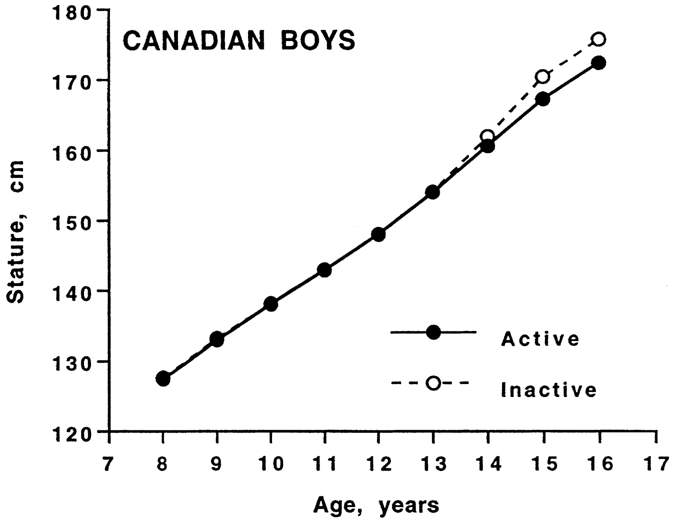


FIGURE 15-1 Mean heights of active and inactive children and adolescents: (A, B) Dutch boys and girls 6–12 years old, (C) Canadian boys 8–16 years old, and (D) Belgian boys 13–18 years old. (Source: Drawn from data reported by Saris et al.,[26] Mirwald and Bailey,[42] and Beunen et al.[3])

Although some early data suggest an increase in stature with regular activity, the observed changes are usually quite small and based on studies that did not control for selection of subjects or maturity status at the time of training or at the time



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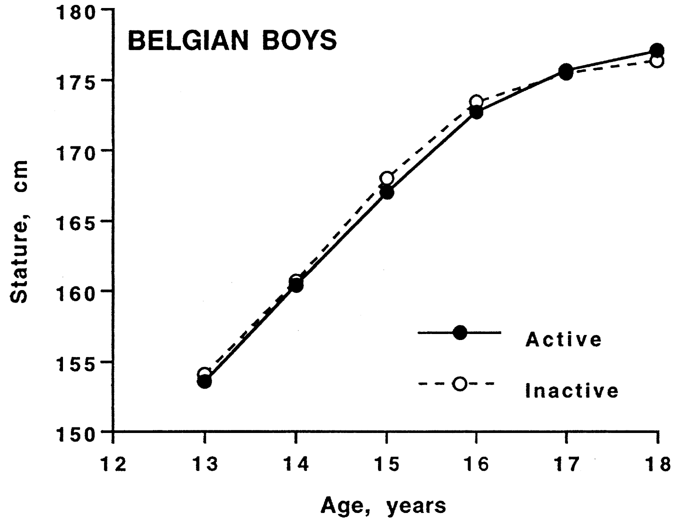

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FIGURE 15-1 *(continued)*

of making the comparisons. Similarly, regular activity does not have a negative effect on growth in height. This is relevant because several studies of young athletes have attributed short stature and a slower growth rate to training for sport (Malina[2]). Some have accepted these observations at face value and concluded that training for athletic competition may slow down or even stunt growth in stature.

However, several important factors are not considered, including selection criteria for some sports and interindividual variation in biological maturation. Some sports select for small body size and even consider parental size in selecting young athletes. Differential timing of the adolescent growth spurt may influence height in short-term studies—a youngster may have his or her growth spurt during an experimental program.

ACTIVITY, BODY WEIGHT, AND BODY COMPOSITION

Differences in body weights of active and inactive boys and girls are generally small and not significant (Figure 15-2). The data vary among studies; for example, the Canadian sample of inactive boys tends to be heavier than active boys, especially during adolescence.

Body weight can be potentially influenced by regular activity, resulting in changes in body composition. Presently available data are derived primarily from the two compartment model:

$$\text{Body weight} = \text{FFM} + \text{FM}$$

where FFM = fat-free mass and FM = fat mass. It is often suggested that regular physical activity is associated with a decrease in FM and an increase in FFM. However, it is difficult to partition effects of training on FFM from expected changes associated with growth and maturation, specifically during adolescence. Both sexes have a significant adolescent spurt in FFM, males more than females (Malina, Bouchard, and Bar-Or[5]).

In the frequently cited study of Parizkova,[6,7] 40 Czech boys were divided into three groups with different physical activity or training programs and were followed longitudinally from 11–18 years old. The active boys ($n = 8$, >6 hr/wk) were selected primarily for basketball ($n = 6$) and athletics ($n = 2$). The other two groups had less regular physical activity: moderate activity ($n = 18$, 4 hr/wk in sport activity but not on a regular basis) and limited activity ($n = 13$, <2 hr/wk in unsystematic sport activity, including physical education). The activity levels of the three groups are described a bit differently by Sprynarova:[8] active—4 hr/wk 11–15 years old, 6 hr/wk 15–18 years old; moderate activity—2 hr/wk 11–15 years old, 3 hr/wk 15–18 years old; limited activity—1 hr/wk 11–15 years old, no regular activity 15–18 years old. The active boys were especially taller than boys in the other two groups throughout the study and heavier from 13–18 years old (Figure 15-3).

The groups differed only slightly in body composition at the beginning of the study, but during the course of the study and at its end, the most active boys had significantly more FFM and less fat than the moderately and least active boys (Figure 15-4). The latter two groups differed only slightly in FFM, but the boys with limited physical activity had greater relative fatness. Given the negligible differences in FFM between the boys with moderate and limited activity, the need for a more intense activity stimulus to produce changes in FFM during growth

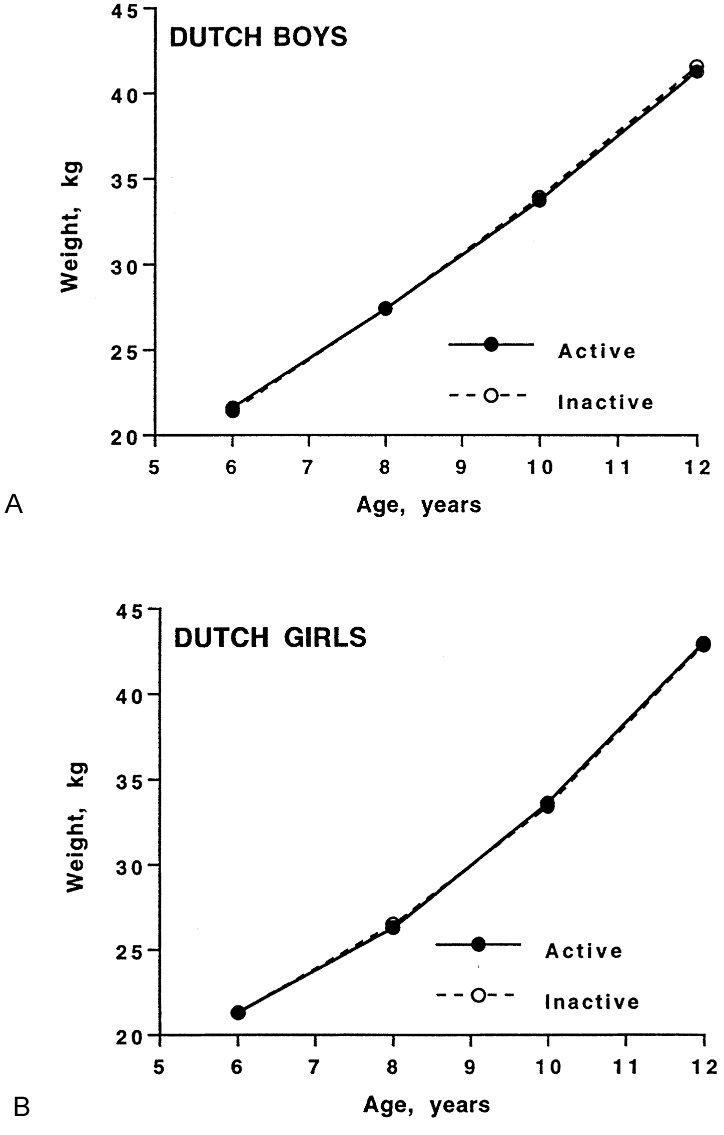
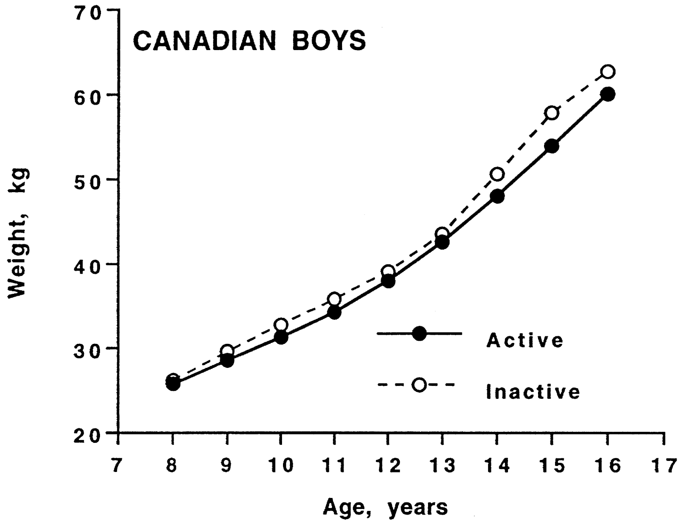


FIGURE 15-2 Mean weights of active and inactive children and adolescents: (A, B) Dutch boys and girls 6–12 years old, (C) Canadian boys 8–16 years old, and (D) Belgian boys 13–18 years old. (Source: Drawn from data reported by Saris et al.,[26] Mirwald and Bailey,[42] and Beunen et al.[3])

is obvious. The active group was also advanced in skeletal maturity and attained peak height velocity at an earlier age, showing a growth pattern characteristic of early maturing boys. Their greater heights and larger gains in FFM compared to



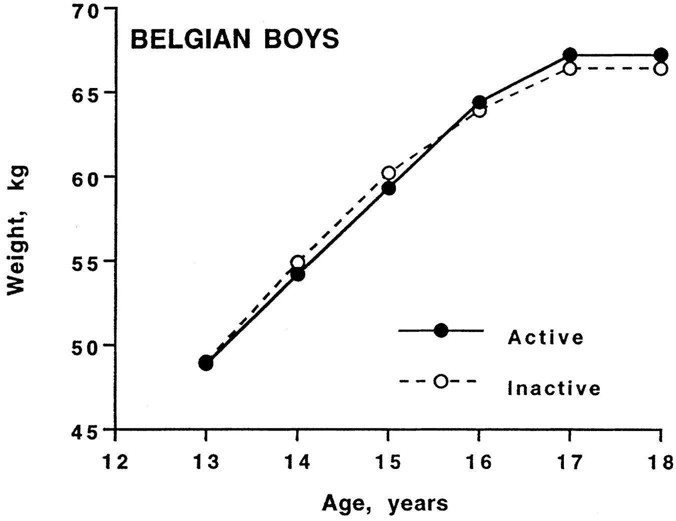


FIGURE 15-2 *(continued)*

the other groups are probably related in part to their advanced maturity status, which was not controlled in the comparisons.

Von Dobeln and Eriksson[9,10] conducted a short-term study of nine boys, 11–13 years old. The program included 5 months of endurance activities designed to increase maximal aerobic power. Significant gains were noted in potassium

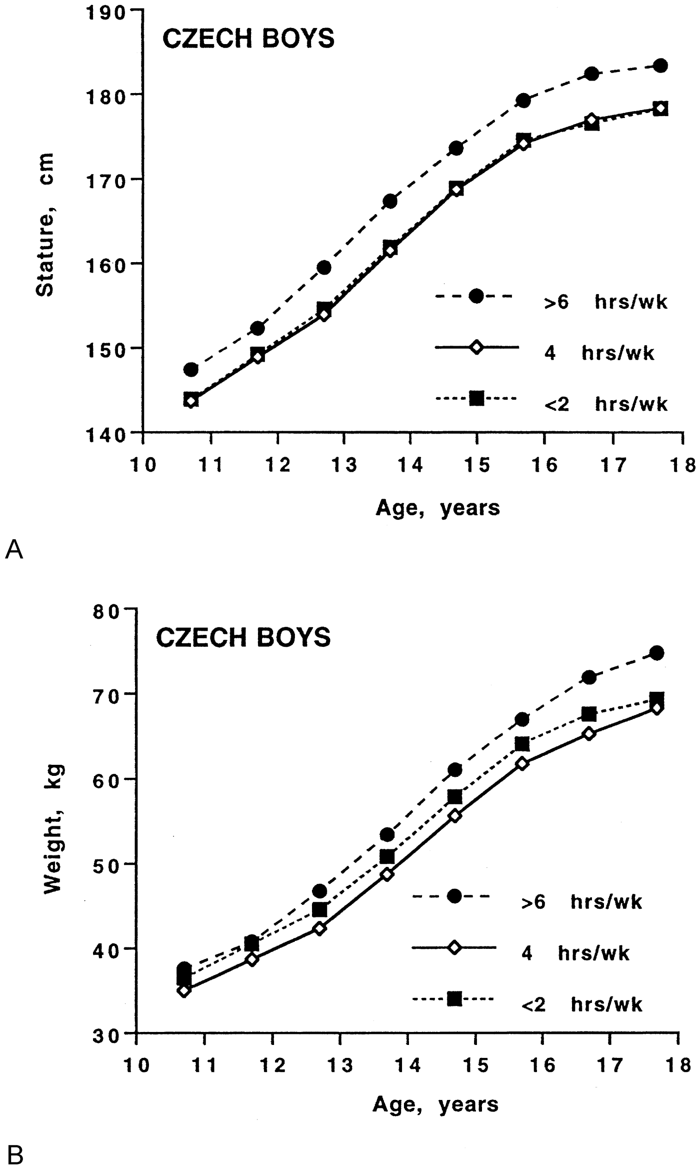


FIGURE 15-3 Mean heights (A) and weights (B) of Czech boys grouped by level of physical activity and followed longitudinally for 8 years. (Source: Drawn from data reported by Parizkova.[6,7])

concentration measured by whole body counting of potassium 40. The boys gained, on average, 0.5 kg in weight and 12 grams of potassium. A 12-gram increase in potassium corresponds to a gain of about 4 kg of muscle mass, which would indi-

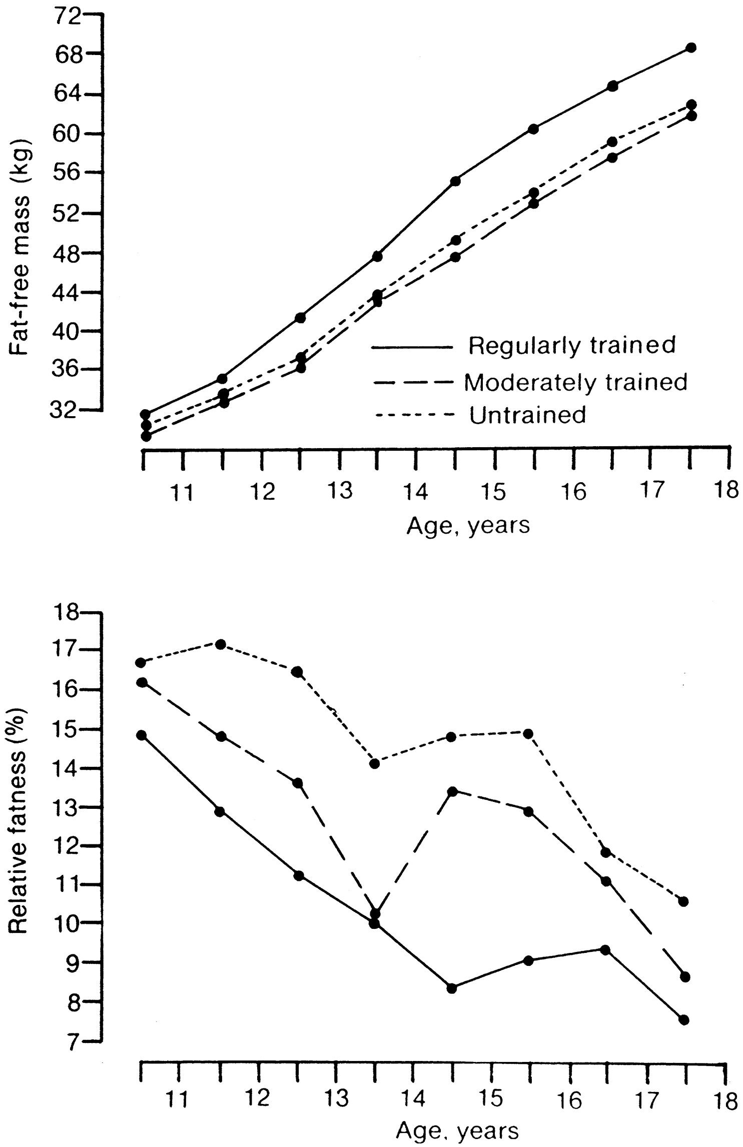


FIGURE 15-4 Estimated fat-free mass (FFM) and percentage fat in Czech boys grouped by level of physical activity and followed longitudinally for 8 years. (Source: Drawn from data reported by Parizkova.[6,7])

cate that the 0.5 kg gain in body weight was accompanied by a loss of about 3 kg of fat during the endurance training program. Relative to growth in height during the experiment, the gain in potassium, an index of FFM and in particular muscle mass, after the training program was 6% greater than expected, whereas the gain in weight was 5% less than expected. The boys gained an average of 3.5 cm in height over the duration of the program (5 months), suggesting that the adolescent spurt probably occurred in some boys during the course of the study. The observed changes in body composition could thus reflect, in part, those that accompany the adolescent spurt in boys and not necessarily the effect of the training program. Further, endurance programs are not often associated with large gains in FFM.

Individual data for the nine boys are summarized in Table 15-1. Three boys of the boys had body weights above one standard deviation of Swedish reference data and five boys lost weight during the training program. With one exception, the largest gains in height and potassium were observed in boys who were in middle to late puberty. A testicular volume less than 4 ml indicates the prepubertal state. Among Swedish boys, the 90th percentiles for the volume of the testes are 4.4 and 9.5 ml at 11 and 12 years, respectively.[11] The oldest prepubertal boy (13.0 years) had a large gain in potassium. The results thus suggest that the gains in potassium, and in turn estimated FFM, and in height are more likely associated with age and sexual maturation rather than the training program.

The studies of Parizkova[6,7] and Von Dobeln and Eriksson[9] illustrate the difficulties partitioning changes in body composition associated with physical activity or short-term training programs from those that accompany normal growth and maturation during male adolescence. Are the changes in body composition associated with regular activity or training greater than changes that accompany growth and maturation? This is not discernable in the presently available data.

The results of these two studies, nevertheless, summarize the information on the potential influence of regular physical activity on body composition during growth. Boys regularly engaged in physical activity programs may have more FFM and less fat than those who are not regularly active. However, are the changes in body composition associated with regular activity greater than those associated

TABLE 15-1 Changes in Body Weight, Height, and Potassium Content in 9 Boys over 0.6 Year, Including 0.5 Years Regular Training

Age (yr)	Testicular Volume (cm^3)	Body Weight (kg)	Height (cm)	Potassium (g)
11.3	<4.8	–1.9	3.4	7.1
11.5	<4.8	–1.1	2.9	7.4
11.6	<4.8	2.0	2.7	8.3
13.0	<4.8	–0.7	1.9	17.4
11.3	4.8–9	–0.4	1.7	8.3
11.6	4.8–9	1.7	3.9	10.1
11.8	>9.0	2.3	4.1	10.8
12.2	>9.0	3.1	5.4	15.6
13.2	>9.0	4.4	5.6	18.1

Note: Age is the midpoint of the 0.6-year interval. Testicular volume was estimated after the training program.

Source: Calculated after Von Dobeln and Eriksson.[9]

with normal growth and maturation? The increase in FFM observed in youth regularly active over a period of several years would seem to suggest an increase greater than that expected with normal growth and maturation. On the other hand, a good deal of the variation in body composition associated with regular physical activity or inactivity is associated with fatness, which fluctuates inversely with the activity stimulus. Fatness tends to decrease during periods of regular activity and increase during periods of inactivity. Thus, changes in response to short-term training programs often reflect fluctuating levels of fatness with minimal or no changes in FFM.

The influence of regular physical activity on fatness is especially apparent in several studies of obese children. For example, a daily program of aerobic activity for 2 years resulted in marked decreases in skinfold thicknesses of obese children.[12] Two short-term training programs, one for 10 weeks and the other for 4 months, show a significant decrease in estimated percentage body fat in obese children 7–11 years.[13,14] However, the persistence of the changes in skinfolds and relative fatness after the cessation of the systematic activity programs was not addressed.

Data comparing the body composition of active and nonactive girls during childhood and adolescence or comparing changes in body composition associated with a program of regular physical activity are limited. Morris et al.[15] compared the body composition of two groups of 9- and 10-year-old girls, one that followed a 10-month training program and the other that followed their normal pattern of physical activity. Girls in the two groups were similar in age, height, weight, body composition, and stage of sexual maturation at the start of the study. The training program included 30 minutes of high-impact aerobic and strength training activities three times per week. After 10 months, the trained girls had a greater gain in estimated lean mass (2.2 ± 1.1 kg) and a smaller increase in fat mass (0.5 ± 0.8 kg) than the girls who followed their normal pattern of physical activity (1.4 ± 1.4 kg lean mass and 1.0 ± 0.8 kg fat mass). Note that both groups gained in lean and fat masses over 10 months; that is, there was on average, no decrease in fatness. There also was considerable overlap between the trained and control groups, but individual differences among the girls after 10 months were, unfortunately, not reported. Although the results are suggestive, they indicate difficulties inherent in attempting to partition growth- from training-related changes in estimated body composition.

The question of sex differences in the responses of FFM and FM to regular programs of physical activity during growth needs further consideration. Evidence for young adults indicates a significant decline in relative fatness and subcutaneous fat and an increase in FFM in males, but not in females, after 15 weeks of high-intensity training on a cycle ergometer.[15]

ACTIVITY AND PHYSIQUE

Methodological variation and individual differences in the stability of somatotype during adolescence confound the evaluation of the effects of regular activity on physique. In the three groups of boys with different training programs from

11 to 18 years old (Figure 15-4), distributions of somatotypes did not differ among the groups, suggesting no effect of the training programs on somatotype (see Malina et al.[5]). The boys changed in somatotype over adolescence, but the changes occurred in a random manner and were not associated with the respective physical activity programs. Therefore, regular physical activity is not a significant factor affecting somatotype during growth.

Some forms of high-intensity resistance training may result in muscular hypertrophy of the body parts specifically exercised; for example, arm and shoulder musculature in responses to weight or resistance training programs. Such changes may, at times, be rather extreme and give the impression of altered physique. However, the changes are rather localized and not sufficient to alter an individual's somatotype. In addition, several months after the cessation of resistance programs, measures of muscular development commonly revert to pretraining values, indicating the transient nature of soft tissue responses to training and the need for regular activity to maintain the beneficial changes.[17] These data are derived from young adults. Corresponding resistance training data for growing and maturing individuals are not available.

ACTIVITY AND SPECIFIC TISSUES

Skeletal, skeletal muscle, and adipose tissues are the primary components of body mass. The skeleton is the framework of the body and the main reservoir of mineral. Skeletal muscle is the major work-producing and oxygen-consuming tissue and the producer of physical activity. Adipose tissue represents energy in stored form.

Skeletal Tissue

Tensile and compressive forces associated with muscular contraction and weight bearing are generally viewed as essential stimuli for skeletal tissue or bone formation and growth. Thus, the intermittent compression of growth plates with weight bearing and physical activity and the localized effects of muscular contraction at the insertions of muscles on bones are apparently essential for bone growth. Regular physical activity during childhood and adolescence is associated with increased bone mineral content, but the osteogenic influence of activity is generally specific to the skeletal sites at which the mechanical strains occur.[18]

Correlational studies indicate a positive relationship between habitual physical activity and bone mineralization. Active children and adolescents have greater bone mineral content and density than those who are less active or inactive. The differences are especially apparent between children and adolescents in the highest and lowest quartiles of estimated physical activity, which is shown in Table 15-2 for girls 8–13 years old. Note that bone mineral accumulation shows an adolescent spurt that occurs after peak height velocity (PHV).[5] More recently, data from a 6-year longitudinal study indicate a significant influence of habitual physical activity on bone mineral accrual during the adolescent growth spurt

TABLE 15-2 Total Body Bone Mineral Content (BMC) and Bone Mineral Density (BMD) in Girls 7–13 Years Old Grouped by Quartile of Physical Activity

	BMC (9 g)		BMD (g/cm^2)	
Quartile of Physical Activity*	Mean	Std Dev	Mean	Std Dev
I	1212	223	0.884	0.06
II	1286	2.8	0.883	0.06
III	1374	231	0.899	0.06
IV	1441	227	0.914	0.05*

*I, lowest; IV, highest.

Estimates of physical activity are based on total energy expenditure adjusted for the body mass index.

Source: Adapted from Ilich et al.[44]

(Table 15-3). Active boys and girls have a greater peak velocity of accrual of bone mineral (g/yr) and a greater amount of bone mineral accumulated during the interval of the growth spurt than normally active boys and girls. The latter, in turn, have greater corresponding bone mineral values than the least active boys and girls. After peak velocity of bone mineral accrual, active boys and girls have 9% and 17% greater total body bone mineral, respectively, than their inactive peers.[19]

TABLE 15-3 Peak Total Body Bone Mineral Content Accrual, Total Body Bone Mineral Content Accrued During the Year Before and After Peak Accrual, and Total Body Bone Mineral 1 Year After Peak Accrual in Boys and Girls Grouped by Level of Habitual Physical Activity

	Peak BMC Accrual (g/yr)		BMC Accrued 1 Yr ± Peak (g)		BMC 1 Yr After Peak (g)	
Activity Status	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Girls						
Inactive	280	50	503	88	1571	199
Average	325	60	577	96	1815	211
Active	367	72	618	112	2003	449
Boys						
Inactive	367	78	640	137	2104	395
Average	395	84	712	140	2198	341
Active	476	81	816	137	2511	355

Inactive are in the lowest quartile of physical activity; average are in the middle two quartiles of activity; active are in the highest quartile of physical activity.[19]

Source: Adapted from Bailey et al.[19]

Differences in bone mineralization are more pronounced for weight-bearing activities than non-weight-bearing activities, and similar trends are apparent in boys and girls.[15,20–22] Among prepubertal boys and girls, those in the highest quartile of weight-bearing physical activity (most active) have an increase in bone mineral 4–7% greater than those in the lowest quartile of weight-bearing activity (least active).[21]

Of particular importance in the context of the beneficial effects of physical activity on skeletal tissue during childhood and adolescence is the observation that bone mineral established during childhood and adolescence is a determinant of bone mineral status in adulthood. Near-adult values of bone mineral are attained in late adolescence, particularly in girls.[5] Further, more active young adults of both sexes generally have more highly mineralized skeletons than nonactive adults. The greater skeletal mineral content in young adulthood presumably represents the beneficial effects of regular physical activity on bone mineralization during growth and maturation.

In contrast to bone mineralization, regular physical activity does not influence bone growth in length.[1,23] The pressure effects of weight-bearing and physical activity are apparently required for normal growth of a bone in length. On the other hand, it has been suggested that excessive pressure may inhibit linear growth, although no evidence has yet been submitted to this effect in healthy, adequately nourished children and adolescents. The delineation of excessive pressure, of course, is problematic.

Skeletal Muscle

Postnatal growth of skeletal muscle tissue is characterized by a generally constant number of fibers and an increase in fiber size and number of nuclei. Some forms of physical activity may result in some hypertrophy of skeletal muscle and increases in contractile proteins and enzyme concentrations. However, the concept of the specificity of physical activity must be emphasized in the responses of muscle tissue to habitual activity programs. Muscular hypertrophy is associated primarily with high-resistance activities, such as weight training, and may not occur with endurance training. Hypertrophy occurs in the existing muscle fibers and not as a result of an increase in the number of fibers. Progressive strength training results in an increase in the size of muscle composed of Type II (fast twitch) fibers, which suggests a specific hypertrophy of Type II fibers. In contrast, endurance training is associated with an increase in the relative area of Type I (slow twitch) fibers and an increase in activities of enzymes associated with the use of fatty acids as a substrate and of oxidative phosphorylation in the mitochondria. Prolonged, intensive strength and endurance programs may have important effects on the proportions of Type I and Type II fibers in the active muscle.[24]

The preceding observations are based on responses of young adult muscle tissue to specific training programs. Corresponding data for growing and maturing children and adolescents are not extensive, but results of several studies are generally similar in direction as those of adults. Resistance training in prepubertal boys and girls results in gains in strength without hypertrophy of muscle tissue. Pubertal boys, on the other hand, experience hypertrophy in conjunction with an increase in strength in response to resistance training.[25] Studies of adults indicate that gains in muscularity associated with resistance training revert to pretraining values when the resistance program is stopped. A question of interest to adolescents relates to the partitioning of training-related changes from those associated with normal growth and maturation, particularly in adolescent boys. Similarly, do the training-related changes in muscle mass in adolescents persist after the training program has stopped? And, how much activity is needed to maintain the training-induced changes?

There is no strong evidence to suggest that fiber type distribution in youth can be changed as a result of specific training protocols. A 5-month endurance training program was associated with no changes in the percentages of Type I and II fibers but with increases in succinate dehydrogenase and phosphofructokinase activities in 11-year-old boys.[10] Results of a comparison of the effects of 3-month sprint and endurance training programs on 16-year-old boys are summarized in Figures 15-5 and 15-6. Both programs did not affect the fiber distribution in muscle tissue. The endurance-trained group showed an increase in the surface area of both Type I and Type II fibers, while the sprint trained group did not (Figure 15-5). The endurance-trained group showed an increase in succinate dehydrogenase activity but no change in phosphofructokinase activity, whereas the sprint-trained group showed an increase in phosphofructokinase and no change in succinate dehydrogenase activity (Figure 15-6).

Corresponding data for young females are not available. The limited data suggest that regular training has the potential to modify the metabolic capacity of muscle in children and youth. However, changes in response to short-term programs are generally not permanent and depend on regular activity for their maintenance.

A unique feature of the study of 16-year-old boys is that the responses of muscle tissue enzymes to 6 months of no supervised training were also monitored. After 6 months of no regular training, enzyme activities returned to levels that did not differ from the pretraining values (Figure 15-6). Although mean levels of enzyme activity after detraining are slightly lower than pretraining means, the differences in this study of adolescent boys are not statistically significant and probably reflect individuality in responses to training and detraining. This observation indicates an important feature of training studies. Monitoring changes associated with training after the training program ceases permits a more accurate evaluation of the effects of training on growth. Changes in response to short-term training programs are generally not permanent and depend on regular activity for their maintenance.

Adipose Tissue

In studies of children and youth, adipose tissue is most often measured subcutaneously in the form of skinfold thicknesses. Cross-sectional data generally indicate thinner skinfolds in active children and adolescents than reference samples.

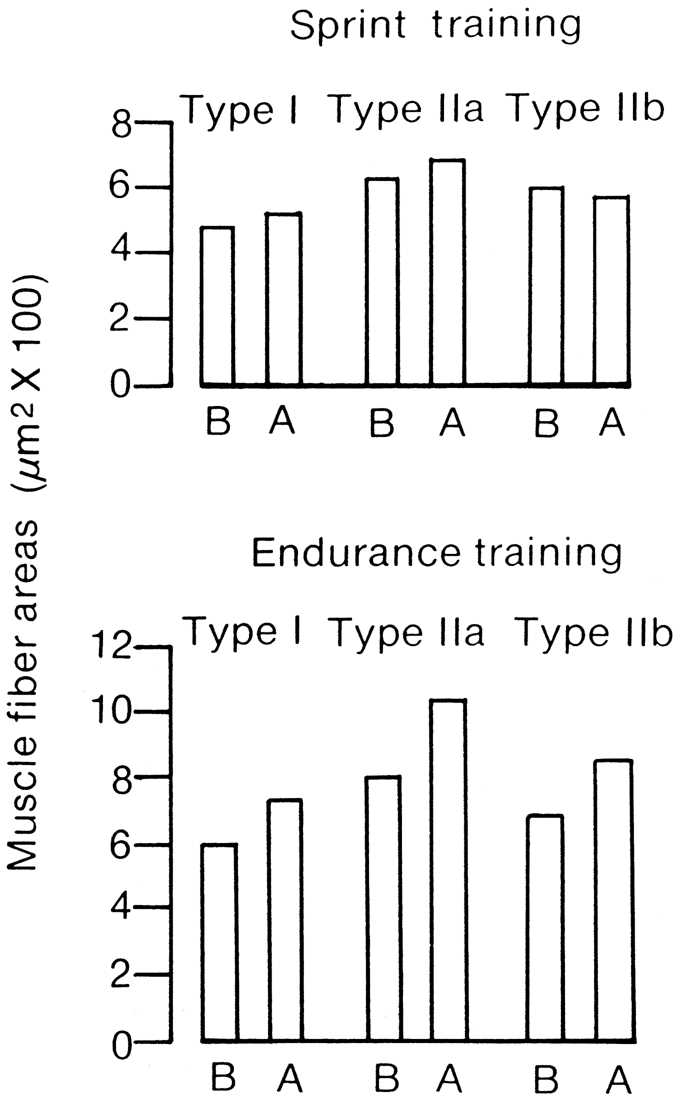
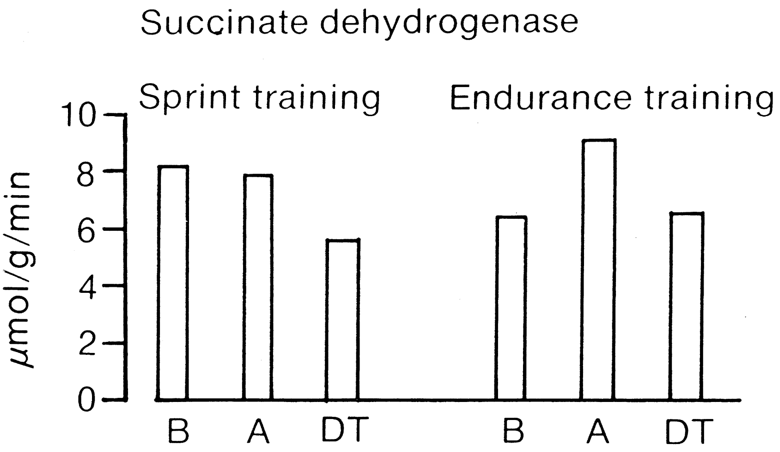


FIGURE 15-5 Changes in muscle fiber areas in 16-year-old boys after 3 months of sprint or endurance training: B = before training; A = after training. (Source: Drawn from data reported by Fournier et al.[43])

On the other hand, longitudinal data for active and nonactive boys and girls followed from 6 to 12 years old[26] and adolescent boys followed from 13 to 18 years old[3] indicate only small and nonsignificant differences between the skinfold thicknesses in active and inactive boys (Figure 15-7). The small differences in mean


Succinate dehydrogenase

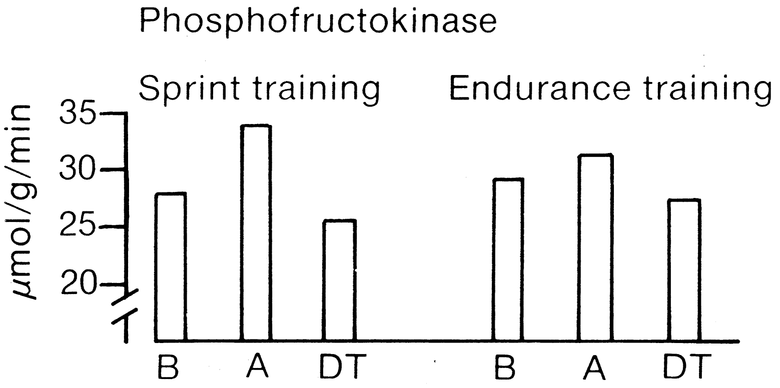

Phosphofructokinase

FIGURE 15-6 Changes in skeletal muscle enzyme activities in 16-year-old boys after 3 months of sprint or endurance training and six months of detraining: B = before training; A = after training; DT = after detraining. (Source: Drawn from data reported by Fournier et al.[43])

skinfold thicknesses are ordinarily well within the range of technical error associated with the measurement of skinfolds.[27] It is likely that more intensive physical activity is essential to modify skinfold thicknesses in children and especially adolescents. In addition, skinfolds change differentially during male adolescence; that is, extremity but not trunk skinfolds ordinarily decline in thickness during male adolescence (Belgian boys in Figure 15-7).

Data dealing with the potential effects of training on subcutaneous fat distribution during growth are limited. Cross-sectional data for male adolescents suggests an association between time spent in vigorous physical activity and proportionally less subcutaneous adipose tissue on the trunk.[28] In young adult males,

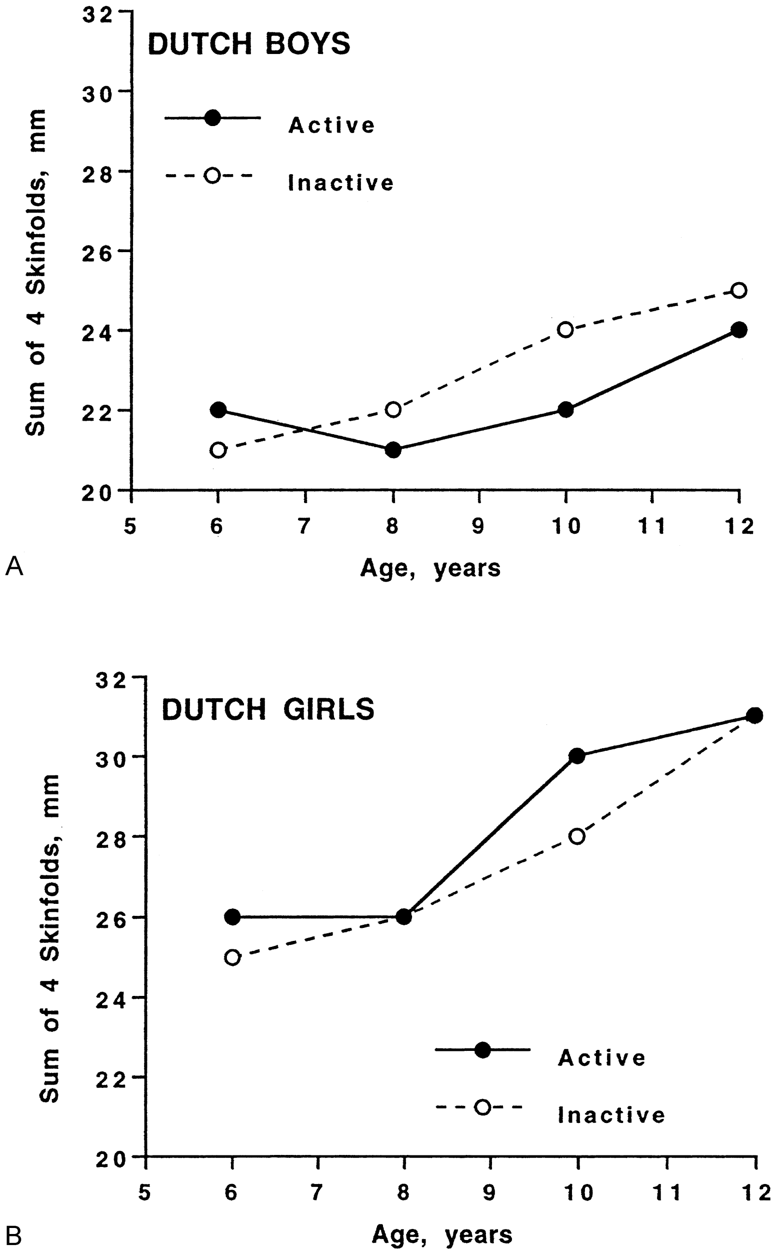
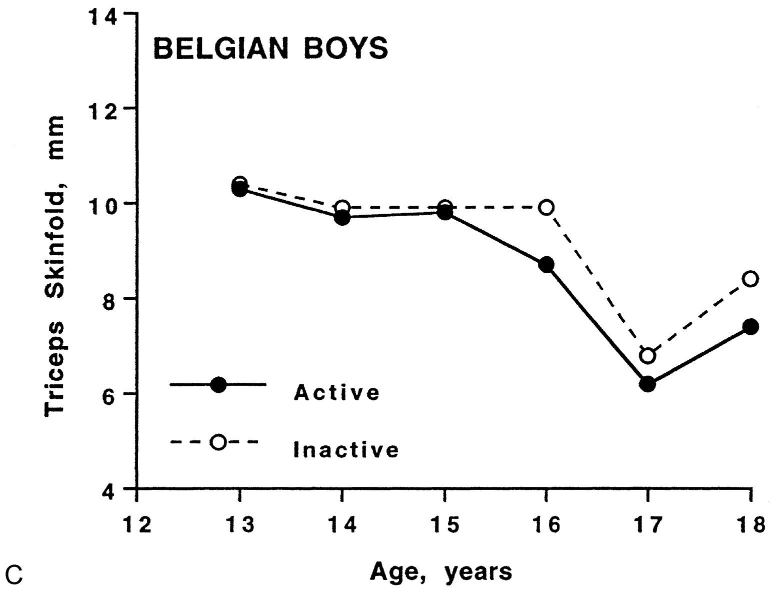


FIGURE 15-7 Mean skinfold thicknesses of active and inactive children and adolescents: (A, B) Dutch boys and girls 6–12 years old, sum of four skinfolds, and (C, D) Belgian boys 13–18 years old, triceps and subscapular skinfolds. (Source: Drawn from data reported by Saris et al.[26] and Beunen et al.[3])



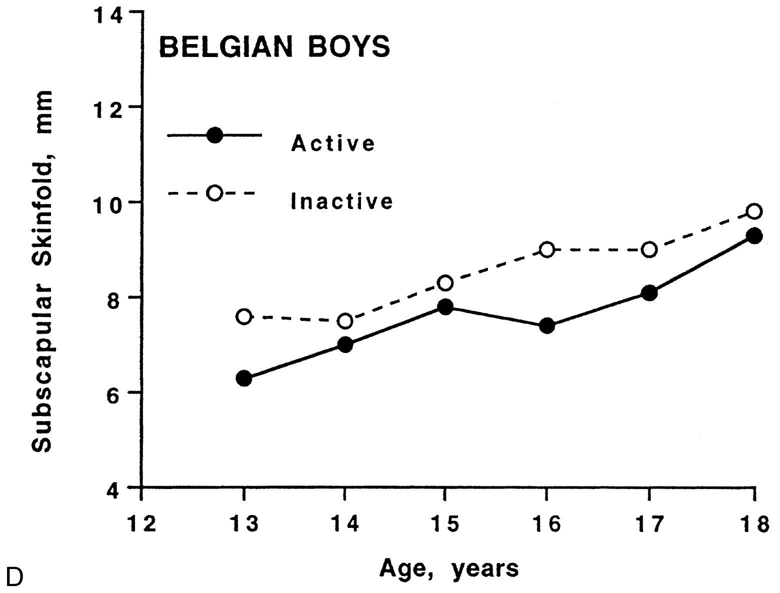


FIGURE 15-7 *(continued)*

intensive aerobic training for 15 and 20 weeks is associated with a greater reduction in trunk than in extremity skinfolds, while corresponding changes in young adult females are evenly distributed between trunk and extremity sites.[16,29] In obese children 7–11 years old, a 4-month physical activity program (5 days/wk, 40 min/session, estimated energy expenditure 226 kcal/session) resulted in minimal change in abdominal visceral adipose tissue but a loss of abdominal subcutaneous adipose tissue. In contrast, obese control subjects who did not participate in the activity program gained in both visceral and subcutaneous abdominal adipose tissue.[30,31] The results for the obese children exposed to the systematic activity program suggest a differential loss subcutaneous adipose tissue in the abdominal region.

Although changes in overall fatness and subcutaneous adipose tissue associated with habitual physical activity are reasonably well documented, information on the effects of regular activity on adipose tissue cellularity and metabolism in children and adolescents is lacking. Evidence from adults indicates that the decrease in fatness with training is attributable solely to a reduction in fat cell size and not to changes in fat cell number. Similar changes in fat cell size and not number also occur with caloric restriction.

Information on the effects of regular activity on adipose tissue cellularity during childhood and adolescence is lacking. Adipose tissue cellularity increases gradually during childhood and then more rapidly with the onset of puberty.[5] The possible effect of regular physical activity programs on adipose tissue cellularity during growth merits consideration. Some experimental evidence suggests that training initiated at about 1 week of age in rats effectively reduces the rate of fat cell proliferation and subsequently results in a reduced number of fat cells and, in turn, fatness later in life. On the other hand, training begun after 7 weeks of age in rats does not affect fat cell number but significantly reduces fat cell size.[32,33] Thus, regular activity plays a significant role in affecting fat cell size; but for activity to affect fat cell number, the program must be initiated very early in the life of rats.

It is not certain whether these experimental observations can be applied to children. The species-specific nature of experimental results must be recognized, in addition to differences between humans and rats. For example, adipocytes of rats and humans differ to some extent in the types of receptors involved in the regulation of lipolysis. Nevertheless, if the results derived from studies of developing rats are applicable to children, they suggest that activity programs must be initiated quite early, perhaps during preschool, to have an influence on adipose tissue cellularity. It may be unrealistic, however, to expect preschool children to engage in regular aerobic activities, although systematic aerobic programs have been used with 3- to 5-year-old children.[34,35]

Regular physical activity also affects adipose tissue metabolism. Trained individuals have an increased ability to mobilize and oxidize fat, which is associated with increased levels of lipolysis. Similar increases in lipolysis also occur in sedentary adults exposed to a 20-week aerobic training program, and there appears to be a sex difference in response. The increase in lipolysis is greater in men than women.[36] Corresponding observations on training and adipose tissue metabolism in children are not presently available. Given the similarity in the response of muscle tissue to regular training in children and adults, it is perhaps reasonable to assume similar metabolic responses of adipose tissue to training in children and adults.

ACTIVITY AND BIOLOGICAL MATURATION

Biological maturation is a highly individual characteristic that is variable in timing (when specific events or changes occur) and tempo (rate or progress). Skeletal maturation is the only system of maturity assessment that spans the period of growth from childhood to adulthood. The hand-wrist area is used most often. Somatic maturation refers to the timing of maximum growth in height during the adolescent growth spurt (age at PHV). Age at PHV can be estimated only from longitudinal data that span adolescence. Sexual maturation is useful only when overt manifestations of the secondary sex characteristics are evident; that is, breast development in girls, genital development in boys, pubic hair in both sexes, and menarche in girls.

It is difficult to quantify the effects of regular physical activity on the various maturity indicators commonly used in growth studies, especially during adolescence. The same hormones regulate somatic, skeletal, and sexual maturation during adolescence, so that regular activity, if it has an effect, should influence the different indicators of maturity in a generally similar manner.

Skeletal Maturation

Although regular physical activity enhances the accrual of bone mineral, it does not influence skeletal maturation of the hand and wrist as it is radiographically assessed in growth studies. Active and nonactive boys followed longitudinally from 13 to 18 years old do not differ in skeletal age.[3]

Somatic Maturation

Age at PHV is not affected by level of habitual physical activity, and presently available data are limited to boys. Small samples of boys classified as physically active and inactive for the years prior to and during the adolescent growth spurt do not differ in estimated ages at PHV (Table 15-4). The magnitude of PHV in active and inactive boys also does not differ and is well within the range of variation in growth velocity during the adolescent spurt. By inference, peak velocity of growth in height during the adolescent growth spurt is not affected by regular activity. Corresponding data are not available for girls classified by level of habitual physical activity.

Sexual Maturation

Information is quite limited on the effects of regular physical activity on sexual maturation. Discussions most often focus on females rather than on both sexes, and specific concern is for the age at menarche, which is a late event in the pubertal

TABLE 15-4 Estimated Mean Ages at Peak Height Velocity (PHV, yr) and Peak Velocities (cm/yr) in Active and Nonactive Adolescent Boys

		Age at PHV		PHV		
Activity Status	Number	Mean	Std Dev	Mean	Std Dev	Reference
Active	14	14.3	1.2	8.7	1.1	Mirwald & Bailey[42]
Inactive	11	14.1	0.7	9.9	1.4	Mirwald & Bailey[42]
Active	32	14.2	0.8	9.4	1.5	Beunen et al.[3]
Inactive	32	14.1	0.8	8.9	2.1	Beunen et al.[3]
Moderate active	19	14.5	1.0	9.7	1.5	Sprynarova[8]
Limited active	12	14.6	1.2	9.8	1.5	Sprynarova[8]
Active	7	13.3*				Kobayashi et al.[45]
Average active	43	13.3*				Kobayashi et al.[45]

Note: The ranges of mean ages at PHV and peak velocities, based on a variety of methods, reported in European and North American longitudinal studies are, respectively, 13.3–14.4 yr and 8.2–10.3 cm/yr.[5]

*These are samples of Japanese boys. Age at PHV occurs earlier, on average, in Japanese than in European and North American adolescents.

sequence. Menarche occurs, on average, a bit more than a year after PHV. Menarche also has cultural and social significance in the lives of adolescent girls.

Some epidemiological data suggest an association with habitual physical activity and later menarche,[37] but contradictory findings are also evident.[38] The association between habitual physical activity and later menarche is not strong and is confounded by other factors. Much of the discussion on the association between physical activity and age at menarche, however, focuses on later mean ages at menarche, which are commonly reported in athletes in many, but not in all sports.[2,39] It is commonly inferred that the later mean ages at menarche are a consequence of regular training for sport before menarche; that is, training "delays" menarche. Use of the term *delay* in the context of physical activity or training is misleading, because it implies that regular physical activity or training "causes" menarche to be later than normal. The data dealing with the inferred relationship between training and later menarche are based on association, are retrospective, and do not permit such a conclusion. Two comprehensive discussions of physical activity and female reproductive health have concluded as follows: "although menarche occurs later in athletes than in nonathletes, it has yet to be shown that exercise delays menarche in anyone,"[40(p. S288)] and "the general consensus is that while menarche occurs later in athletes than in nonathletes, the relationship is not causal and is confounded by other factors."[41(pp. 2–3)]

Longitudinal data on the sexual maturation of habitually active and nonactive boys and girls are not available. The available data, which are of mixed quality, focus on young athletes. The growth and maturity characteristics of young athletes and potential effects of intensive training for sport are discussed in more detail in Malina.[2]

CONCLUSION

The developing organism clearly adapts to the stresses imposed by physical activity. The stimulus of regular physical activity and responses to the activity are, to a large extent, not sufficient to significantly alter the processes of growth and maturation as they are ordinarily monitored. Therefore, physical activity has no apparent effect on stature and maturation as ordinarily assessed in growth studies. It can, however, be an important factor in the regulation of body weight and specifically fatness. Regular physical activity also functions to enhance skeletal mineral and density and is a significant factor in the structural and functional integrity of skeletal muscle tissue. Effects of activity programs on adipose and muscle tissues are reversible and depend on regular activity for their maintenance. Effects of activity programs on skeletal muscle tissue are also specific to the type of program, endurance or resistance.

Physical activity is presumably important in normal growth and maturation, but it is not known how much activity is necessary. Apparently, the day-to-day activities of childhood and adolescence are adequate to maintain the integrity of growth and maturation processes, with the possible exception of adipose tissue. Physical inactivity in combination with a chronically excessive energy intake is associated with greater levels of fatness. Both are the primary contributors to the current epidemic of obesity in children and adolescents in developed countries of the world. Regulation of fatness is more effectively done through combined physical activity and dietary monitoring, although it is not easily achieved and relapse into excess body fat is the rule rather than the exception.

SUGGESTED READING

Blimkie CJR, Sale DG. Strength development and trainability during childhood. In: Van Praagh E (ed). Pediatric Anaerobic Performance. Champaign, IL: Human Kinetics, 1998:193–224. (A good discussion of the effects of strength or resistance training on the development of muscular strength during childhood and adolescence.)

Malina RM. The effects of exercise on specific tissues, dimensions and functions during growth. Stud Phys Anthropol. 1979;5:21–52. (An earlier review of exercise and growth that includes references to many earlier studies.)

Malina RM. Growth and maturation: Normal variation and the effects of training. In: Gisolfi CV, Lamb DR (eds). Perspectives in Exercise Science and Sports Medicine. Vol 2. Youth, Exercise, and Sport. Indianapolis: Benchmark

Press, 1989:223–265. (A review of the potential effects of exercise on growth and maturation in the context of normal variation.)

Malina RM. Growth, exercise, fitness, and later outcomes. In: Bouchard C, Shephard RJ, Stephens T, Sutton JR, McPherson BD (eds). Exercise, Fitness, and Health: A Consensus of Current Knowledge. Champaign, IL: Human Kinetics, 1990:637–653. (A summary of physical activity as a factor affecting growth and physical fitness during childhood and adolescence and potential tracking into adulthood.)

Malina RM. Physical activity: Relationship to growth, maturation, and physical fitness. In: Bouchard C, Shephard RJ, Stephens T (eds). Physical Activity, Fitness, and Health. Champaign, IL: Human Kinetics, 1994:918–930. (This is a sequel to Malina, 1990.)

Sale D. Strength and power training during youth. In: Gisolfi CV, Lamb DR (eds). Perspectives in Exercise Science and Sports Medicine. Vol. 2. Youth, Exercise, and Sport. Indianapolis: Benchmark Press, 1989:165–216. (A comprehensive discussion of strength training on growth of muscle and more specifically on strength.)

Steinhaus AH. Chronic effects of exercise. Physiol Rev. 1933;13:103–147. (A classic review that includes summaries of early experimental programs on various animal species.)

REFERENCES

References preceded by an asterisk (*) include more comprehensive discussions and bibliographies. The others are specifically cited in the text.

1. *Rarick GL. Exercise and growth. In: Johnson WR (ed). Science and Medicine of Exercise and Sports. New York: Harper and Brothers, 1960:440–465. (One of the first comprehensive reviews of exercise and growth.)
2. *Malina RM. Growth and maturation of young athletes—Is training for sport a factor? In: Chan K-M, Micheli LJ (eds). Sports and Children. Hong Kong: Williams and Wilkins Asia-Pacific, 1998:133–161. (A summary of the growth and maturity status of young athletes, and a discussion of the potential effects of training.)
3. *Beunen GP, Malina RM, Renson R, Simons J, Ostyn M, Lefevre J. Physical activity and growth, maturation and performance: A longitudinal study. Med Sci Sports Exer. 1992;24:576–585. (A comparison of habitually active and inactive boys followed longitudinally through adolescence and includes measures of growth, skeletal maturation, and motor performance.)
4. *Malina RM. Physical growth and biological maturation of young athletes. Exer Sport Sci Rev. 1994;22:389–433. (A summary of growth and maturity characteristics of young athletes by sport.)
5. *Malina RM, Bouchard C, Bar-Or O. Growth, Maturation, and Physical Activity, 2nd ed. Champaign, IL: Human Kinetics, 2002. (A comprehensive textbook of growth and maturation with special sections on motor performance and physical activity, among other factors.)
6. Parizkova J. Longitudinal study of the relationship between body composition and anthropometric characteristics in boys during growth and development. Glasnik Antropoloskog Drustva Jugoslavije. 1970;7:33–38.

7. *Parizkova J. Body Fat and Physical Fitness. The Hague: Martinus Nijhoff, 1977. (A summary of several studies of children and adolescents in the context of physical activity and body composition.)
8. Sprynarova S. The influence of training on physical and functional growth before, during and after puberty. Euro J Appl Physiol. 1987;56:719–724.
9. Von Dobeln W, Eriksson BO. Physical training, maximal oxygen uptake and dimensions of the oxygen transporting and metabolizing organs in boys 11–13 years of age. Acta Paediatr Scan. 1972;61:653–660.
10. Eriksson BO. Physical training, oxygen supply and muscle metabolism in 11–13 year old boys. Acta Physiol Scan. 1972;(Suppl):384.
11. Taranger J, Engstrom I, Lichenstein H, Svennberg-Redegen I. Somatic pubertal development. Acta Paediatr Scan. 1976;258(Suppl):121–135.
12. Sasaki J, Shindo M, Tanaka H, Ando M, Arakawa K. A long-term aerobic exercise program decreases the obesity index and increases the high density lipoprotein cholesterol concentration in obese children. Inter J Obes. 1987;11:339–345.
13. Gutin B, Cucuzzo N, Islam S, Smith C, Stachura ME. Physical training, lifestyle education, and coronary risk factors in obese girls. Med Sci Sports Exer. 1996;28:19–23.
14. Gutin B, Owens S, Slavens G, Riggs S, Treiber F. Effects of physical training on heart period variability in obese children. J Pediatr. 1997;130:938–943.
15. Morris FL, Naughton GA, Gibbs JL, Carlson JS, Wark JD. Prospective 10-month exercise intervention in premenarcheal girls: Positive effects on bone and lean mass. J Bone Miner Res. 1997;12:1453–1462.
16. Tremblay A, Despres JP, Bouchard C. Alteration in body fat and fat distribution with exercise. In: Bouchard C, Johnston FE (eds). Fat Distribution During Growth and Later Health Outcomes. New York: Liss, 1988:297–312.
17. *Malina RM, Rarick GL. Growth, physique, and motor performance. In: Rarick GL (ed). Physical Activity, Human Growth and Development. New York: Academic Press, 1973:125–153. (An overview of methods of assessing physique in the context of growth and performance.)
18. *Kannus P, Sievanen H, Vuori I. Physical loading, exercise, and bone. Bone. 1996;18:1S–3S. (A concise summary of the stress of loading on bone tissue.)
19. Bailey DA, McKay HA, Mirwald RL, Crocker PRE, Faulkner RA. A 6-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: The University of Saskatchewan Bone Mineral Accrual Study. J Bone Miner Res. 1999;14:1672–1679.
20. Slemenda CW, Miller JZ, Hui SL, Reister TK, Johnston CC. Role of physical activity in the development of skeletal mass in children. J Bone Miner Res. 1991;6:1227–1233.
21. Slemenda CW, Reister TK, Hui SL, Miller JA, Christian JC, Johnston CC. Influences on skeletal mineralization in children and adolescents: Evidence for varying effects of sexual maturation and physical activity. J Pediatr. 1994;125:201–207.
22. Nordstrom P, Pettersson U, Lorentzon R. Type of physical activity, muscle strength, and pubertal stage as determinants of bone mineral density and bone area in adolescent boys. J Bone Miner Res. 1998;13:1141–1148.
23. *Steinhaus AH. Chronic effects of exercise. Physiol Rev. 1933;13:103–147. (A classic review that includes summaries of early experimental programs on various animal species.)
24. *Saltin B, Gollnick PD. Skeletal muscle adaptability: Significance for metabolism and performance. In: Peachey LD (ed). Handbook of Physiology, Section 10, Skeletal Muscle. Bethesda, MD: American Physiological Society, 1983:555–631. (A comprehensive review of basic skeletal muscle physiology.)
25. *Sale D. Strength and power training during youth. In: Gisolfi CV, Lamb DR (eds). Perspectives in Exercise Science and Sports Medicine. Vol. 2. Youth, Exercise, and Sport. Indianapolis: Benchmark Press, 1989:165–216. (A comprehensive discussion of strength training on growth of muscle and more specifically on strength.)

26. Saris WHM, Elvers JWH, van't Hof MA, Binkhorst RA. Changes in physical activity of children aged 6 to 12 years. In: Rutenfranz J, Mocellin R, Klimt F (eds). Children and Exercise XII. Champaign, IL: Human Kinetics, 1986:121–130.
27. *Malina RM. Anthropometry. In: Maud PJ, Foster C (eds). Physiological Assessment of Human Fitness. Champaign, IL: Human Kinetics, 1995:205–219. (Includes a comprehensive table of measurement errors in anthropometry.)
28. Dionne I, Almeras N, Bouchard C, Tremblay A. The association between vigorous physical activities and fat deposition in male adolescents. Med Sci Sports Exer. 2000;32:392–395.
29. Despres JP, Bouchard C, Tremblay A, Savard R, Marcotte M. Effects of aerobic training on fat distribution in male subjects. Med Sci Sports Exer. 1985;17:113–118.
30. Gutin B, Owens S. Role of exercise intervention in improving body fat distribution and risk profile in children. Amer J Hum Biol. 1999;11:237–247.
31. *Gutin B, Humphries M. Exercise, body composition, and health in children. In: Lamb D, Murray R (eds). Perspectives in Exercise Science and Sports Medicine. Vol. 11. Exercise, Nutrition, and Weight Control. Carmel, IN: Cooper, 1998:295–347. (An overview of activity and body composition of children and especially obese children.)
32. Oscai LB, Spirakis CN, Wolff CA, Beck RJ. Effects of exercise and of food restriction on adipose tissue cellularity. J Lipid Res. 1972;13:588–592.
33. Oscai LB, Babirak SP, McGarr JA, Spirakis CN. Effect of exercise on adipose tissue cellularity. Federation Proc. 1974;33:1956–1958.
34. Alpert B, Field T, Goldstein S. Perry S. Aerobics enhances cardiovascular fitness and agility in preschoolers. Health Psychol. 1990;9:48–56.
35. Mo-suwan L, Pongprapai S, Junjana C, Puetpaiboon A. Effects of a controlled trial of a school-based exercise program on the obesity indexes of preschool children. Amer J Clin Nutrit. 1998;68:1006–1011.
36. Despres J-P, Bouchard C, Savard R, Tremblay A, Marcotte M, Theriault G. The effect of a 20-week endurance training program on adipose-tissue morphology and lipolysis in men and women. Metabolism. 1984;33:235–239.
37. Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. Amer J Epidemiol. 1993;138:217–224.
38. Moisan J, Meyer F, Gingras S. Leisure physical activity and age at menarche. Med Sci Sports Exer. 1991;23:1170–1175.
39. *Malina RM. Menarche in athletes: A synthesis and hypothesis. Ann Hum Biol. 1983;10:1–24. (A summary of ages at menarche in athletes with a critical discussion of factors that influence this maturational landmark.)
40. *Loucks AB, Vaitukaitis J, Cameron JL, Rogol AD, Skrinar G, Warren MP, et al. The reproductive system and exercise in women. Med Sci Sports Exer. 1992;24:S288–S293. (This is a summary of a consensus discussion of the effects of exercise on the female reproductive system.)
41. *Clapp JF, Little KD. The interaction between regular exercise and selected aspects of women's health. Amer J Obstet Gynecol. 1995;173:2–9. (A review.)
42. Mirwald RL, Bailey DA. Maximal Aerobic Power. London, Ontario: Sports Dynamics, 1986.
43. Fournier M, Ricci J, Taylor AW, Ferguson RJ, Montpetit RR, Chairman BR. Skeletal muscle adaptation in adolescent boys: Sprint and endurance training and detraining. Med Sci Sports Exer. 1982;14:453–456.
44. Ilich JZ, Skugor M, Hangartner T, Baoshe A, Matkovic V. Relation of nutrition, body composition and physical activity to skeletal development: A cross-sectional study in preadolescent females. J Amer Coll Nutrit. 1998;17:136–147.
45. Kobayashi K, Kitamura K, Miura M, Sodeyama H, Murase Y, Miyashita M, et al. Aerobic power as related to body growth and training in Japanese boys: A longitudinal study. J Appl Physiol. 1978;44:666–672.

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THE ASSESSMENT OF HUMAN GROWTH

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INTRODUCTION

Common thoughts as to how to assess a child's physical growth center around measures of weight and stature. These measurements are easy to collect in a variety of settings, and they are concepts to which children, their parents, and society can relate. All parents want to know how big or tall their child is, since a large body size generally indicates good health. Children also want to know how tall they are relative to their peers, because being tall implies a higher social status. Large, tall children are more frequently chosen by teachers and peers for assignments that relate to status at school, especially in sports. Weight and stature are the most common measures taken from children in school, at home, or at a health clinic. However, we now have the technology and equipment to assess more than just the physical size of a growing child, we can now assess the growth of a child's body composition.

We need to measure the amounts or levels of adipose tissue in children because obesity is currently the most prevalent disease of childhood.[1,2] Today, a big child may be an obese child rather than one who is healthy and well fed, as in the past. Obesity in childhood is strongly linked with subsequent overweight and obesity in adulthood and its cardiovascular consequences.[3] We can also measure the amount of muscle tissue in children, and for the first time, we can measure the amount and density of bone in growing children. Both these tissues can be assessed with a minuscule exposure to radiation. Measures of bone mineral content (BMC) and bone mineral density (BMD) allow us to identify children with low levels (frequently due to a low calcium intake), who are at potential risk for osteoporosis later in adulthood.[4] Measuring the growth status of a child's body composition provides an opportunity to treat risk factors for some chronic adult diseases at their conception, when treatment can be most effective.

During the past decade, the assessment of child growth has expanded to include the traditional external measures of a child's body and more recently its internal composition. The linking of measures of body size in indices, such as the body mass index (BMI, a screening tool for obesity) to direct measures of body composition in children and the availability of new and improved body composition technology like bioelectrical impedance and dual energy X-ray systems, have facilitated this expanded scientific and clinical interest in growth assessment. This chapter presents techniques for measuring growth in body size and discusses current methods of assessing the growth of a child's body composition. The techniques described are used throughout the world in research and clinical settings where child growth and body compositions are assessed.

BODY SIZE ASSESSMENTS

Accurate and reliable measurements of physical body size are necessary to assess the growth status of a child. Measurement techniques for growth assessment are now clearly described on videotapes available from the National Center for Health Statistics,[5] the World Health Organization (De Onis, personal communication), and on several websites. These media clearly demonstrate standardized methods for collecting physical growth measures of infants and children. The descriptions in this chapter are similar, if not identical, to those presented or described in several of these media formats and to the techniques used to collect corresponding measurements in the Third National Health and Nutrition Examination Survey (NHANES III),[6] the current NHANES, and the World Health Organizations Multicentre Growth Reference Study.[7] These descriptions are also similar to corresponding methods listed in the *Anthropometric Standardization Reference Manual*.[8] Regardless of the specific descriptions or standardized techniques used, the collection of accurate growth data requires the assistance of two health technicians for the roles of examiner and recorder. The examiner positions the child and takes each measurement. The recorder assists the examiner in taking the measurements by helping position the child and equipment properly.

Standardized techniques are important to allow comparisons of growth and body composition data among studies and especially for assessing the growth status of a child using reference data from the NHANES surveys. For these techniques, it is recommended that physical size measurements of a child be taken on the right side of the body, but they can also be taken on the left side. The right side is used in all national reference surveys in the United States, while the left side is used in European and WHO surveys. Lohman, Martorell, and Roche, writing in the *Anthropometric Standardization Reference Manual*,[8] maintain that the choice of side for measurement "matters very little, if at all. In all cases [of studies to investigate this question] the bias associated with side of measurement was less than measurement error." However, the significant differences that did result from the research studies all reflected larger values on the right side of the body and particularly so for upper limb dimensions. This would imply an exercise effect that might be significant in some research designs. The biological importance of such differences should be judged within the context of the research design and appropriate allowances made to either measure the left side, or the right side, or both.

The most useful measures of the physical size of a child are recumbent length from birth to 3 years old, stature from age 3 years, head circumference from birth to 3 years old, and weight at every age. Recumbent length and stature reflect the amount of linear growth that occurs due to the increase in the size of the skeleton. Head circumference is an indirect measure of the brain's growth, which attains approximately 95% of its adult size in the first 5 years of life. Weight is an indicator of the general growth of all body tissues and is the most critical of all growth measurements.

Growth is an anabolic process so a positive trend in successive weight, stature, and head circumference values generally indicates that a child's growth is approximately normal. If the trend in successive measures is none or negative, then a thorough clinical examination is necessary and needs to be conducted expeditiously. There are specific reference data and percentile charts to determine the normalcy of a child's growth status and the rate of growth in length, stature, weight, and head circumference. The newest U.S. growth charts now include percentiles for BMI as well, to assess a child's level of obesity.[9]

MEASUREMENTS OF PHYSICAL SIZE

Recumbent Length

Recumbent length is measured on an accurate device, and two people should be used. One person positions the infant or child's head against the headboard with the child looking straight up. The other person positions the child down the length of the center of the device with the shoulders and hips perpendicular to the trunk. The second person straightens the legs and brings the footboard up against the soles of the feet.

Stature

Stature is measured on an accurate, stable device properly mounted to a wall, such as a measuring stick or a nonstretchable tape attached to a flat, vertical surface, or some form of a right-angle headboard. If an anthropometer is used, it needs to be held vertically (i.e., at right angles to the level surface of the floor). The child stands upright without assistance and with bare feet, heels close together, legs straight, arms at the sides, and shoulders relaxed. The child looks straight ahead so that the line of vision is perpendicular to the body or in the Frankfort horizontal plane position. The slide or headpiece is lowered onto the crown of the head with sufficient pressure to compress the hair. Hair ornaments, buns, braids, and the like are removed as necessary to obtain an accurate measurement. Stature is measured at maximum inspiration. The measurer's eyes should be level with the headpiece to avoid reading errors due to parallax. Stature can be measured in children as young as 2 years of age, but most children cannot maintain an erect stature until about 3 years of age. For overweight children, with excess adipose tissue on the buttocks, the body is positioned vertically erect above and below the waist.

Head Circumference

Head circumference is measured with an inelastic tape between birth and 3–5 years old. The technique will vary slightly between children, but certain points are important. The tape is level across the front of the head with the infant or child held in a sitting position. The tape is positioned just over the eyebrows. The greatest circumference of the head is located by moving the tape across the back of the head, and pulling the tape tight to take the reading.

Weight

Weight is taken on an accurate device with the child wearing minimal clothing. Preferably, a child is weighed nude after voiding with only a minimal amount of underclothing. If the child is clothed in undergarments, 0.1 kg is subtracted from the reading. Spring-type bathroom scales are not recommended because they are not accurate for research or clinical purposes. There are a variety of infant scales and beam balance and digital scales for larger children.

Other Body Measurements

Additional measures to consider in assessing physical size are the midarm and abdominal circumferences and the thickness of subcutaneous adipose tissue from skinfolds. These additional measures are related primarily to determining levels of body fatness. Midarm circumference is an index of the underlying fat and muscle tissue. Abdominal circumference is an indicator of the development of abdominal obesity that is increasingly prevalent in children.[10] Subcutaneous adipose tissue can be measured at a variety of locations on the body as the thickness of a skinfold. Large values for midarm and abdominal circumferences and skinfolds are positively correlated with total and percent body fat in children.[11] There is also a high degree of correlation among body circumferences and among skinfold thickness. The majority of the obesity in children is due to an excess of subcutaneous adipose tissue.

Midarm Circumference

For all circumferences, a tape measure is positioned around a specific part of the body in a plane parallel to the floor or perpendicular to the body segment being measured. As a general rule, the tape rests flat on the surface of the skin. The tension of the tape is snug (i.e., not too tight or loose and not tight enough to compress the surface of the skin).

The arm is flexed 90° at the elbow with the palm facing up. The midpoint between the upper edge of the posterior border of the acromial process of the scapula and the tip of the olecranon is located and marked on the posterior surface. With the arm then hanging free at the side, the measuring tape is placed around the upper arm at the level of the marked point perpendicular to the long axis of the upper arm.

Abdominal Circumference

At the highest point of the iliac crest determined in the midline of the side of the body, the measuring tape is placed around the abdomen in a horizontal plane at this level marked on the side of the trunk. The plane of the tape is parallel to the floor, and the measurement is made at normal respiration.

Triceps and Subscapular Skinfolds

For skinfolds, a fold of skin and underlying subcutaneous adipose tissue are gently grasped between the thumb and forefingers. The amount grasped depends on the thickness of the subcutaneous adipose tissue. The examiner gently grasps enough skin and adipose tissue to form a distinct fold that separates from the underlying muscle above the place where the measurement is taken. The sides of the fold are roughly parallel; the jaws of the calipers are placed at the marked level, perpendicular to the length of the fold; and the skinfold thickness is measured while the fingers continue to hold the skinfold. The actual measurement is read from the caliper about 2–3 seconds after the caliper tension is released. Two of the most common sites for measuring skinfolds are on the back of the arm over the triceps muscle and just below the scapula.

For the triceps skinfold, the marked midpoint for the midarm circumference is located on the posterior surface of the upper arm. The jaws of the calipers are opened and placed at the marked level, on the back of the upper arm perpendicular to the length of the fold and the skinfold thickness measured.

For the subscapular skinfold, the shoulders and arms are relaxed, and the inferior angle of the scapula is located. A fold of skin and subcutaneous adipose tissue directly below (1.0 cm) and medial to the inferior angle is grasped. The skinfold forms a line about 45° below the horizontal extending diagonally toward the elbow. The jaws of the caliper are opened and placed perpendicular to the length of the fold lateral to the fingers with the top jaw of the caliper on the mark over the inferior angle of the scapula.

Several other body measurements can be taken for studies of specific aspects of growth and physical size or in statistical models for estimating body composition.[8,12] For example, breadths at the shoulders and hips describe sex differences, while other breadths at the wrist and elbow are related to frame size.[8,13] There are also other skinfold sites where sex differences in body fatness are measurable as there are other locations for body circumferences. These other measurements are not generally useful in assessing the growth status of a healthy child, but they have potential uses for growth assessments from obese, handicapped, or children with specific clinical conditions.[14] These measurements may also be informative in specific research studies related to obesity or growth disorders. Descriptions of techniques for these other measurements, if needed, can be found in the *Anthropometric Standardization Reference Manual.*[8]

Clinical Growth Assessments

Measuring the body size of children suffering from clinical conditions, such as obesity, cerebral palsy, contractures, braces or mental retardation, is difficult. The heterogeneity of the physical expression of these conditions and problems among affected children can be large. There are no recommended or standardized methods and only limited or no specific reference data available for many of these groups of children.[15] If the child can stand, standard methods can be applied; otherwise recumbent and anthropometric methods are recommended.[16,17] Recumbent anthropometric techniques are applicable to children regardless of their ability to stand or assume an erect posture. Recumbent measurements are reliable and accurate, and values from recumbent measurements are not systematically different in value from corresponding standing techniques.[18] Measures of weight in nonambulatory children require special equipment, such as bed or wheelchair scales. Recumbent length can sometimes be taken from handicapped children. Stature cannot be measured accurately in most nonambulatory or handicapped children, but the estimation of stature from recumbent knee height with known errors is the best method at present for providing this information for children 6 years old and older.[19]

Knee Height

Knee height is used to estimate stature for which published equations are available for normal and handicapped children.[17,19] The fixed blade of a large sliding caliper is placed under the heel of the leg just below the lateral malleolus of the fibula. The knee and ankle are both positioned at a 90° angle for this measurement. The shaft of the caliper is held parallel to the shaft of the tibia, so that the caliper passes over the lateral malleolus of the fibula and just posterior to the head of the fibula. The movable blade of the caliper is moved to the anterior surface of the thigh above the condyles of the femur.

ASSESSMENT OF BODY COMPOSITION

There are direct and indirect methods of assessing a child's body composition. Direct methods measure a specific chemical or anatomical part of the body at the elemental, molecular, or cellular level.[20] Direct methods are invasive and difficult to justify in healthy children. Indirect methods are less accurate measures of body components at the molecular or tissue level and include models to estimate body composition. Neutron activation, computed tomography, and magnetic resonance imaging are examples of direct methods that provide accurate measures of the body's composition but are used mostly in clinical situations.

Indirect methods frequently use measures of body weight and length, bioelectrical impedance, and measures of skinfolds or circumferences in mathematical or statistical models. The application of these methods and models is based on assumptions regarding the density of body tissues, the concentration of water and electrolytes in fat free mass (FFM), and biological interrelationships among normal individuals in levels of lean and fat tissues that have been validated against results from direct methods. These assumptions are generally derived from samples of adults and may not be applicable to children.

Body composition in children (and adults) has been estimated most frequently using a two-compartment model that divides the body into fat and fat-free components based on assumptions that the densities of fat and lean tissues are constant.[21] The density of fat varies little among individuals at any age, but the density of lean or FFM varies considerably, depending on its hydration and the relative proportions of muscle and bone, both of which grow and vary in size and amounts among children with age, gender, race, and level of maturation. These interindividual variations affect the density of lean tissue and increase errors in estimates of body composition in children.[22] The body density value can combine with a measure of bone density from dual-energy X ray (DXA) and the volume of total body water in multicompartment models to calculate body fatness in children as proposed by Lohman.[22] Accuracy is improved by using a multicompartment model for body composition that accounts for differences among growing children in their levels of fatness, muscle mass, age, ethnicity, and sex.[23]

In the past, one limitation in the utility of assessing body composition in children was the unavailability of reference data. This is no longer the case for adolescence,[24] but there are still limits on references for the body composition of infants and children. Recently, BIA prediction equations for total body water (TBW) and FFM have been developed[25] that are applicable to the use of national distribution for TBW, FFM, total body fat (TBF), and percent of body fat (%BF) for adolescents 12–19 years of age.[26]

BODY COMPOSITION METHODS

Body composition methods available to assess the growth status of the amount of bone muscle and fat in a child's body vary with the age of the child. Those methods that require some level of subject performance are usually of limited value in small children under 10 years old. "Passive" methods do not require a level of physical performance but may require a child to remain still for a few to several minutes. These methods are applicable to children on an individual basis.

Body Density

Hydrodensitometry estimates body composition using the overall density of the body. This method requires a measure of body weight in air and a measure of body volume using the Archimedes method of fluid displacement (underwater weighing) or more recently air displacement. It is necessary for a child to be familiar with water for underwater weighing, because the child submerges underwater and exhales the air in the lungs to residual volume. Weight underwater is measured and residual lung volume is also determined with a computerized spirometer. These measured values are used to calculate body density using the equations of Siri[21] or Brozek.[27] The air displacement methods are not as difficult as underwater weighing but still require a certain level of cooperation by the child to complete the testing.

Dual Energy X-Ray Absorptiometry

DXA quantifies amounts of bone, muscle, and adipose tissue via total and regional analysis of body composition in children.[28,29] In comparison to other indirect body composition methods, DXA has the advantage of a relative independence from age-, ethnic-, and gender-sensitive assumptions for bone. However, one must recognize its inherent problems and the assumptions regarding levels of hydration, potassium content, or tissue density in regard to the estimation of soft tissue values.[30] For young children and infants, specific pediatric software is available for scan analysis from some manufacturers. It is necessary for a child to remain still while lying supine on the DXA table for between 4 and 15 minutes, depending on the size and age of the child and the type of DXA machine used. On the printout, the values for lean or soft tissue may need to be corrected for bone mineral content to calculate FFM.

Bioelectric Impedance

The use of bioelectric impedance to estimate body composition is based on the impedance of the body to low-amplitude alternating electric current. In the human body, the current is conducted by electrolytes in body fluids, most of which are contained in the FFM.[31] Whole-body impedance is measured from the right wrist to the right ankle with stature as the length of the conductor. The majority of the research in bioelectrical impedance has been with adults. This method has been applied to children in only a limited number of studies.[23,25] In general, this method is as accurate and precise in children as in adults. Bioelectrical impedance machines are now commercially available; however, the precision of these commercial instruments with children is potentially questionable.

STATISTICAL METHODS OF BODY COMPOSITION

Statistical methods of determining body composition require the development of regression equations with TBF, %BF, or FFM as the dependent variable and anthropometric and bioelectrical impedance variables as the independent or predictor variables. The use of a predictor variable depends on its biological and statistical relationships to the dependent variable. Potential variables for predicting body composition commonly include measures of weight, stature, body circumferences, skinfold thicknesses, and bioelectric impedance.

Regression Analysis

Several regression methods are available to develop an equation to predict body composition. Regression methods should not be used when multicollinearity exists or the predictor variables are interrelated, because the variance of the regression coefficients will be inflated and the precision and accuracy will be poor.[32] In these instances, a maximum R^2 or an all-possible subset of regression procedure are appropriate analytical choices. A prediction equation also depends on several assumptions about the distributions of the dependent variable and its bivariate relationships with the predictor variables. This relationship must be linear, or the derived equation will have large errors and perform poorly when compared with independent samples. It is also assumed that the dependent variable is normally distributed to allow statistical inferences about the significance of the regression parameters.

A prediction equation should have a good fit to the data from which the equation was generated. The larger the R^2 value, the greater the proportion of the variance explained and the better the fit. The root mean square error (RMSE) is a measure of precision and the goodness of fit of an equation. RMSE values can also be standardized, called the *coefficient of variation* (CV), which is useful in comparing prediction equations with different response variables.[12]

In general, the larger the sample, the more precise and accurate the developed prediction equation. The necessary sample size depends on the number of predictor variables, the bivariate relationships among the dependent variable and the predictor variables, and the variance of the dependent variable in the cross-validation sample.

Cross-validation is the application of a prediction equation to an independent sample that matches closely the circumstances in which the equation is likely to be applied. In the cross-validation sample, the dependent and predictor variables need to be collected using the same instruments and procedures used in the sample where the equation was derived. The pure error is a measure of the performance of a prediction equation when cross-validated. Pure error is the square root of the sum of the squared differences between the observed and predicted values divided by the number of subjects in the cross-validation sample.[12] The smaller the pure error, the greater the accuracy of the equation when applied to an independent sample.

Limitations and Sources of Error

It is important in interpreting results from any assessment of growth and body composition to be cognizant of the numerous and sometimes severe limitations of the methods and models used. The limits of anthropometry are in their gross nature. Stature and weight in BMI are only an index of body composition. A skinfold measures only a compressible amount of subcutaneous adipose tissue thickness at a specific location. The combination of the variances of the measurements affects the specific use of anthropometry. However, its utility as a screening tool or in describing the percentile location of a child's growth or selective fatness is unmatched, considering the amount of available reference data.

For growth data to be of value, the measurements must be accurate and reliable. There are several limitations and sources of error for anthropometry and body composition. The child being measured and the person taking the measurements are the major sources of measurement error. This is especially true for infants, young children, and handicapped children who cannot cooperate adequately. Because of the small size of the measurement values in young children, the error is proportionally larger than in older children. Accuracy is how near a measurement is to its true value. The reliability of a measurement is the difference among repeated values for the same measurement. A measurement repeated three times with the same reading each time has perfect reliability. Measurements may be reliable but inaccurate because of poor or uncalibrated equipment or the use of improper technique. Repeated measurements that differ from one another are less reliable but normal.

Frequently only a single observer is available, but he or she should always take two readings for each measurement, record both readings, and compute an average. A limit should also be placed on the allowable difference between pairs of readings for a measurement; for example, 0.2 kg for weight, 1.0 cm for stature, and 0.5 cm for head circumference. If one of these limits is exceeded for a measurement, that pair should be taken again. If the limit is still exceeded, an average of all four readings is recorded for a measurement and the average computed. The taking of at least a pair of readings for a measurement provides an average value that is closer to the true value than a single measurement. It is also important to make notes about the level of cooperation of a child when measurements are taken. An uncooperative child is difficult if not impossible to measure, and this can seriously affect the values of the measurements, especially serial measurements and increments computed. The presence of a note about the child may aid in the interpretation of data collected for the same child at the next visit.

The limitations for body composition vary from method to method, but each method when performed at its best has an error of at least 2–3% body fat when compared with corresponding results from other methods.[22] These limitations and their subsequent errors are in part because the growth of the body composition in a child is a very dynamic process.

Body density is limited to those children who can physically perform the procedures. This is frequently a child older than 10 years. Increased errors and a loss of accuracy come from those children less inclined or able to exert a maximum level of performance or due to deterioration in physical performance. DXAis hampered by physical limits that affect large children in terms of body weight, length, thickness, and width. Also several different manufacturers produce DXA devices and each uses a different technology, so intermachine differences can appear in estimates of body composition for the same individuals. This difference among manufacturers on the body composition of children is not clearly understood.

The limitation of bioelectrical impedance is that estimates of FFM from prediction equations are based on an assumed average hydration of FFM of 73%. However, this percentage occurs at maturity, after childhood. One accuracy of a prediction equation is reduced when it is applied to other samples, and the reduction can be substantial. Factors that affect the accuracy include the validity of the dependent variable, the measurement error of the predictor and dependent variables, the biological and statistical relationships among the predictor variables and between the predictor variables and the dependent variable, the statistical methods employed to formulate the equation, and the size and the nature of the sample.[12]

A variety of equipment for measuring growth status and body composition is available from numerous suppliers and manufacturers. A listing of suppliers and vendors is not provided, as such a list is quickly out of date. Some equipment is more accurate, reliable, easy to use, and lower in cost than others. Knowledge of the proper equipment for collecting growth data also includes its maintenance and calibration. For example, the accuracy of scales should be checked with a set of standard weights at least two or three times a year. Body composition equipment should be calibrated on a regular basis, and annual maintenance is recommended.

This chapter presents information regarding old and newer methods of assessing the physical growth status of children. Today a measure of growth can and should include an amount of body composition along with usual measures of stature and weight. Because of the increased prevalence of obesity around the world, these growth assessments should include a computation of BMI at a minimum and possibly triceps and subscapular skinfolds. If possible, more informative measures of body composition should be considered. Growth assessment is a means of determining the nutritional health of a child. For many parts of the world, undernutrition has been surpassed by the health consequences of overnutrition.

REFERENCES

1. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents: The National Health and Nutrition Examination Surveys, 1963–1991. Arch Pediatr Adoles Med. 1995;149:1085–1091.
2. Dietz WH, Franks AL, Marks JS. The obesity problem. N Engl J Med. 1998;338:1157.
3. Guo SS, Chumlea WCC. Tracking of body mass index in children in relation to overweight in adulthood. Amer J Clin Nutrit. 1999;70:145S–148S.
4. Matkovic V, Jelic T, Wardlaw G, Ilich JZ, Goel PK, Wright JK, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis—Inference from a cross-sectional model. J Clin Invest. 1994;93:799–808.
5. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination 1988–1994. Washington, DC: National Center for Health Statistics, 1994.
6. U.S. Department of Health and Human Services. National Health and Nutrition Examination Survey III. Anthropometric Procedures (videotape). Washington, DC: U.S. Dept. of Health and Human Services—Public Health Services, 1996.
7. De Onis M, Garza C. Time for a new growth reference. Pediatr. 1997;100:1–2.
8. Lohman T, Martorell R, Roche AF. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics, 1998.
9. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC Growth Charts: United States. Adv Data. 2000;314:1–28.
10. Goran MI, Gower BA. Relation between visceral fat and disease risk in children and adolescents. Amer J Clin Nutrit. 1999;70:149S–156S.
11. Roche A, Siervogel R, Chumlea W, Webb P. Grading body fatness from limited anthropometric data. Amer J Clin Nutrit. 1981;34:2831–2838.
12. Guo SS, Chumlea WCC. Statistical methods for the development and testing of predictive equations. In: Roche AF, Heymsfield SB, Lohman TG (eds). Human Body Composition. Champaign, IL: Human Kinetics, 1996:191–202.
13. Himes JH. Considering frame size in nutritional assessment. In: Himes JH (ed). Anthropometric Assessment of Nutritional Status. New York: Wiley-Liss, 1991:141–150.
14. Chumlea WCC, Guo SS. Physical growth and development. In: Samour PW, Helm KK (eds). The Handbook of Pediatric Nutrition. Gaithersburg, MD: Aspen Publishers, 1999:3–15.
15. Cronk CE, Crocker AC, Pueschel SM, Shea AM, Zackai E. Growth charts for children with Down syndrome: 1 month to 18 years of age. Pediatr. 1988;61:102–110.
16. Chumlea WC. Assessing growth and nutritional status in children with developmental disabilities. Consult Diet Newsl. 1986;11:23–25.
17. Stevenson RD. Use of segmental measures to estimate stature in children with cerebral palsy. Arch Pediatr Adoles Med. 1995;149:658–662.
18. Chumlea WC, Roche AF. Nutritional anthropometric assessment of non-ambulatory persons using recumbent techniques. Amer J Phys Anthrop. 1984;63:146.
19. Chumlea WCC, Guo SS, Steinbaugh ML. The prediction of stature from knee height for black and white adults and children, with application to the mobility-impaired. J Amer Diet Assn. 1994;94:1385–1391.
20. Heymsfield SB, Lichtman S, Baumgartner RN, et al. Body composition of humans: Comparison of two improved four compartment models that differ in expense, technical complexity, and radiation exposure. Amer J Clin Nutrit. 1992;1:52–58.
21. Siri W. Body composition from fluid spaces and density analysis of methods. In: Brozek J, Henshcel A (eds). Techniques for Measuring Body Composition. Washington, DC: National Academy Press, 1961:223–244.
22. Lohman TG. Applicability of body composition techniques and constants for children and youths. Exer Sports Sci Rev. 1986;14:325–357.
23. Guo SS, Roche AF, Houtkooper L. Fat-free mass in children and young adults from bioelectric impedance and anthropometric variables. Amer J Clin Nutrit. 1989;50:435–443.

24. Maynard LM, Guo SS, Chumlea WC, et al. Total body and regional bone mineral content and area bone mineral density in children aged 8 to 18 years: From the Fels Longitudinal Study. Amer J Clin Nutrit. 1998;68:1111–1117.
25. Guo SS. Development of bioelectrical impedance prediction equations for body composition using a multicomponent model for use in epidemiological surveys. Amer J Clin Nutrit. (in press).
26. Chumlea WC, Guo SS, Kuczmarski RJ, et al. Body composition estimates from NHANES III bioelectrical impedance data. Int J Obes. (in press).
27. Brozek J. Body composition: models and estimation equations. Amer J Phys Anthropol. 1966;24:239–246.
28. Lukaski HC. Soft tissue composition and bone mineral status—Evaluation by dual-energy X-ray absorptiometry. J Nutrit. 1993;123(Suppl 2):438–443.
29. Kohrt WM. Body composition by DXA: Tried and true? Med Sci Sports Exer. 1995;27:1349–1353.
30. Roubenoff R, Kehayias J, Dawsonhughes B, Heymsfield S. Use of dual-energy X-ray absorptiometry in body-composition studies—Not yet a gold standard. Amer J Clin Nutrit. 1993;58:589–591.
31. Chumlea W, Guo S. Bioelectrical impedance and body composition: Present status and future directions. Nutrit Rev. 1994;52:123–131.
32. Montgomery DC, Peck EA. Introduction to Linear Regression Analysis. New York: John Wiley, 1981.

17

ASSESSMENT OF MATURATION

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INTRODUCTION

The process of maturation is continuous throughout life—it begins at conception and ends at death. This chapter concentrates on the assessment of the process of maturation from birth to childhood, that part of the total process intimately linked to physical growth. It is important, therefore, to differentiate between "growth" and "maturation." Bogin[1] defined the former as "a quantitative increase in size or mass," such as increases in height or weight. Development or maturation, on the other hand, is defined as "a progression of changes, either quantitative or qualitative, that lead from an undifferentiated or immature state to a highly organised, specialised, and mature state." The end point of maturation, within the context of the growth, is the attainment of adulthood, which I define as a "functionally mature individual." Functional maturation, in a biological context, implies the ability to successfully procreate and raise offspring, who themselves will successfully procreate. We know that, in addition to the obvious functional necessities of sperm and ova production, reproductive success within any mammalian society is also dependent on a variety of morphological characteristics, such as size and shape. The too short or too tall, the too fat or too thin are unlikely to achieve the same reproductive success as those within an "acceptable" range of height and weight values that are themselves dependent on the norms in a particular society. Thus, in its broadest context, maturation *and* growth are intimately related and both must reach functional and structural endpoints that provide the opportunity for successful procreation.

INITIAL CONSIDERATIONS

To understand how maturation can be assessed, it is important to first appreciate that maturation is not linked to time in a chronological sense. In other words, 1 year of chronological time is not equivalent to 1 year of maturational "time." This is perhaps best illustrated in Figure 17-1 in which three boys and three girls of precisely the same chronological ages demonstrate dramatically different degrees of maturity, as evidenced by the appearance of secondary sexual characteristics. In addition they exhibit changes in the proportion and distribution of subcutaneous fat and the development of the skeleton and musculature that result in sexually dimorphic body shapes in adulthood. While each individual has passed through the same chronological time span they have done so at very different rates of maturation.

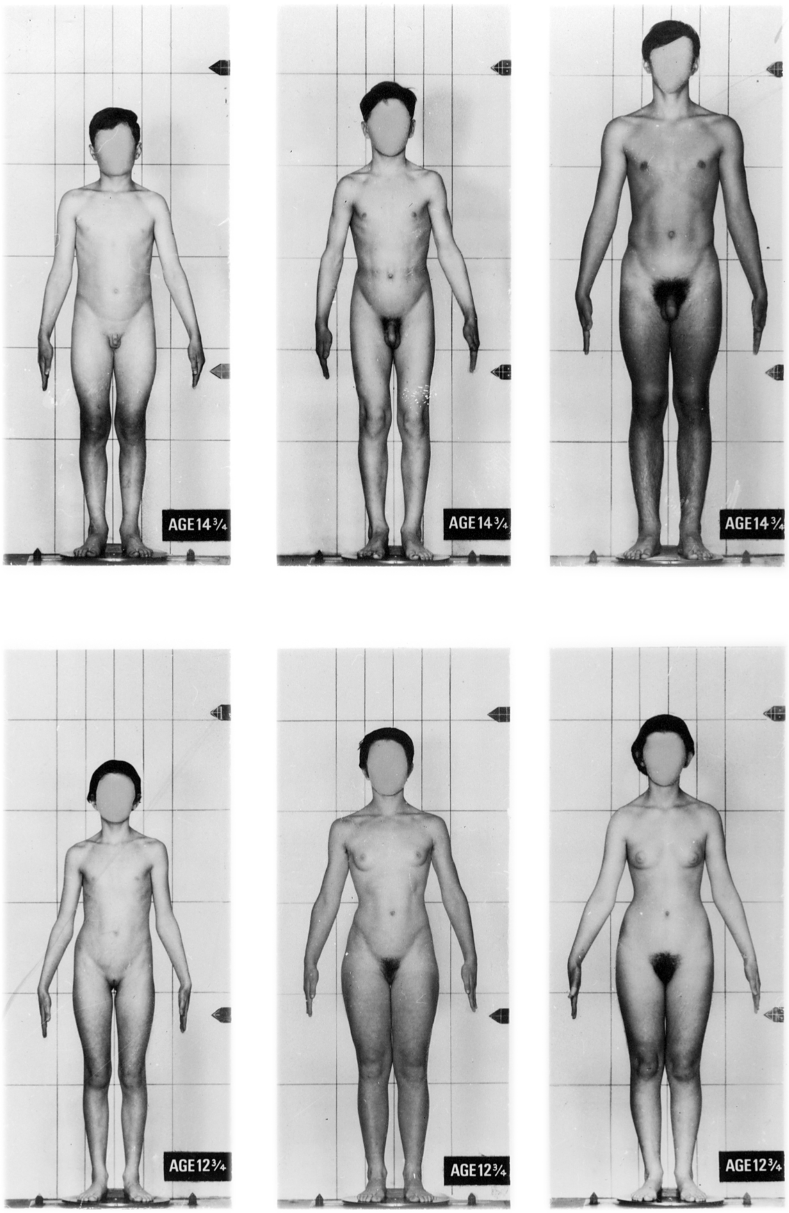
Second, it is important to appreciate that maturation is most often assessed by the identification of "maturity indicators." Such indicators are discrete events or stages recognizable within the continuous changes that occur during the process of maturation. Thus, the indicators that identify breast or pubic hair development divide the *continuous* changes that occur into discrete stages.

Third, we must appreciate that there is variability of maturation *within* the individual. For instance, while skeletal and secondary sexual maturation are associated, they are not correlated so significantly that one can categorically associate a particular stage of sexual maturation with a particular skeletal "age."[2,3] In the closest association, of skeletal age to menarcheal age, it is possible to state that a girl with a skeletal age less than 12 years is unlikely to have experienced menarche and that one with a skeletal age of 15 years is likely to be postmenarcheal. We cannot state with any real degree of confidence that the association of these two maturational processes is closer than that.

Fourth, within a particular maturational process, such as sexual maturation, it is apparent that different structures (e.g., genitalia and pubic hair) will not necessarily be at precisely the same level of maturity. Thus, we have a process of "uneven maturation."

Fifth, there is clear sexual dimorphism within human growth and maturation such that females tend to be advanced relative to males at any particular chronological age. In Figure 17-1, for instance, the females are aged exactly 12.75 years and the males are aged 14.75 years, yet their levels of secondary sexual development are similar.

Sixth, maturation is not related to size except in very general terms; a small human is likely to be a child and thus less mature than a large human, who is more likely to be an adult. As the ages of the two individuals approach each other so the distinction between size and maturity narrows and disappears such that, within a group of similar maturity, there will be a range of sizes and within a group of similar size there will be a range of maturity levels. Therefore, when maturation is assessed, size must be controlled for or excluded from the assessment method.


AGE14¾
AGE14¾
AGE14¾
AGE12¾
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AGE12¾

FIGURE 17-1 Three boys and three girls photographed at the same chronological ages within sex: 12.75 years for girls and 14.75 years for boys. (Source: Tanner JM. Growth and endocrinology of the adolescent. In: Gardner L (ed). Endocrine and Genetic Diseases of Childhood, 2nd ed. Philadelphia: W. B. Saunders, 1975.)

These six considerations—the relationship of maturity to time, the quantification of the continuous process of maturation by using discrete events, the relative independence of different processes of maturation within the individual, the appreciation of uneven maturation, sexual dimorphism, and the lack of a relationship between maturity and size—have governed the development of techniques for the assessment of maturation.

Concept of Time

Roy M. Acheson[4] elegantly described the problem of "time" within the development of skeletal maturity assessment methods:

> *Because maturation is distinct from growth it merits a distinct scale of measurement, indeed the whole basis of the medical and scientific interest it attracts is that it does not proceed at the same rate in the various members of a random group of healthy children. The corollary of this is that the unit of measurement, "the skeletal year," does not have the same meaning for any two healthy children, nor even . . . does a skeletal year necessarily have the same meaning for two bones in a single healthy child.*

The core problem is the use of an age scale to represent maturity. This fails at the extreme because no particular age can be associated with full maturity and, prior to full maturity, because of the lack of a constant relationship between maturity and time both between and within the sexes. Therefore, when using the Greulich-Pyle atlas technique for skeletal maturity[5] one is faced with the final "standards" for males and females that correspond to an "age" of 18 years but in fact represent full maturity or the maturity to be found in any individual who has achieved total epiphyseal fusion regardless of his or her actual chronological age.

To overcome this problem in the assessment of skeletal maturity by moving away from an "age"-based method, Acheson[6,7] and Tanner and his colleagues[8–10] developed the "bone-specific scoring" techniques, in which numerical scores were assigned to each bone rather than a bone "age." Acheson's earlier attempt, which became known as the *Oxford method*, simply gave scores of 1, 2, 3, and so forth to each stage. However, this scoring method did not account for the fact that the differences between scales were not equivalent: The "difference" between stage 1 and stage 2 was not necessarily equivalent, in terms of the advancement of maturity, to the difference between stages 2 and 3. Tanner's basic principle was that the development of each single bone, within a selected area, reflected the *single* process of maturation. Ideally, the scores from each bone in a particular area should be the same and the common score would be the individual's maturity. However such scores would not be the same because of the large gaps between successive events in a single bone. Therefore, the scoring process would need to minimize the overall disagreement between different bones. The disagreement is measured by the sum of squares of deviations of bone scores about the mean score, and this is the sum minimized. To avoid what Tanner described as the "trivial solution" of perfect agreement by giving the same scores to each stage, the scores were constrained on a scale of 0–100; that is, each bone starts at 0 and matures at 100. In essence, each maturity indicator is rated on a maturity scale from 0% maturity to

100% maturity. Without dwelling on the mathematics, which are given in detail by Tanner and his colleagues,[10] the principle is important and should be applied to any *new* system of assessing maturity. In addition, the bone-specific scoring approach can be applied to an appropriate sample of radiographs from any population to derive maturity norms.

The principle of scoring maturity indicators was later applied to the assessment of dental maturity by Demirijan, Goldstein, and Tanner,[11] but to date, has not been applied to other attempts at maturational assessment, such as secondary sexual development. The reason for this apparent neglect may be that we still use the staging system originally developed by Nicholson and Harley[12] and modified by Tanner, Whitehouse, and Healy in 1962.[9] Only five stages are used within any particular area, and these are often difficult to assess accurately. Also, secondary sexual development takes place over a relatively short period of time, say between 10 and 17 years in girls, compared to the birth to adulthood temporal basis of skeletal maturity. Therefore, one is faced with fewer maturity indicators within a short period of time and the application of a scoring technique has seemed inappropriate. However, other aspects of skeletal maturity may lend themselves to a scoring system. Cranial suture closure, for instance, has rarely been investigated as an indicator of maturity in children. Yet this latter technique is important in biological anthropology, in which the maturity of skeletal remains is of forensic interest to determine chronological age, and of course, in paleoanthropology, in which the maturity of a "subadult" fossil has a bearing on the interpretation of the morphology of the individual. Meindl and Lovejoy[13] described a "revised method" for determining skeletal age, using the lateral-anterior sutures. They use a scoring system that is the equivalent of Acheson's for the Oxford method and, in so doing, repeat the erroneous concept that differences between scores are equivalent; that is, the difference between stages 1 and 2 is the same as that between stages 2 and 3. Suture closure is a suitable area for the application of the methods developed by auxologists and would have broad relevance within biological anthropology.

Maturity Indicators

The development of the concept of maturity indicators by Wingate Todd,[14] based on the pioneering work of Milo Hellman in 1928,[15] was fundamental in developing methods to accurately assess skeletal maturity. Prior to the identification of maturity indicators, skeletal maturity was assessed by the "number of ossification centers" method, in which a count was made, either from the hand and wrist[16,17] or from a skeletal survey of each child,[18] of the number of centers present or absent in the total skeleton. Alternatively, planimetry was used to assess the total amount of bony tissue apparent in radiographs.[19–21] The former method failed because of a lack of appreciation of the fact that the order of appearance of ossification centers is largely under genetic control[22] and the latter method because only the carpus was used, which as we now appreciate, is not representative of overall maturity.

I define a *maturity indicator* as a definable and sequential change in any part or parts of the body that is characteristic of the progression of the body from immaturity to maturity. Skeletal development provides the clearest example of such maturity indicators.

Figure 17-2 illustrates the maturity indicators for the developing radius identified independently by two groups of researchers: Greulich and Pyle (GP)[5] and Tanner, Whitehouse, and Healy (TW).[9] Both groups examined the development of the radius apparent in radiographs of the left hand and wrist of children from birth to adult maturity. The former group identified 11 indicators whereas Tanner et al.[9] described 8. It is apparent, however, that visually, at least, the indicators of Tanner et al.[9] are not dramatically different from those of Greulich and Pyle.[5] Indeed, it is actually very important that these indicators are similar. If the two groups of researchers had arrived at very different maturity indicators within the same skeletal area, then each group would have been identifying *different* aspects of maturation and would cast doubt on our ability to recognize the process of maturation. The similarity of the indicators defined by these two *independent* research groups illustrates that they were recognizing the same process and using similar criteria to measure its progression. Regardless of the particular maturational process under investigation, the identification of maturity indicators is fundamental to quantifying that process and arriving at measures of individual and population variation.

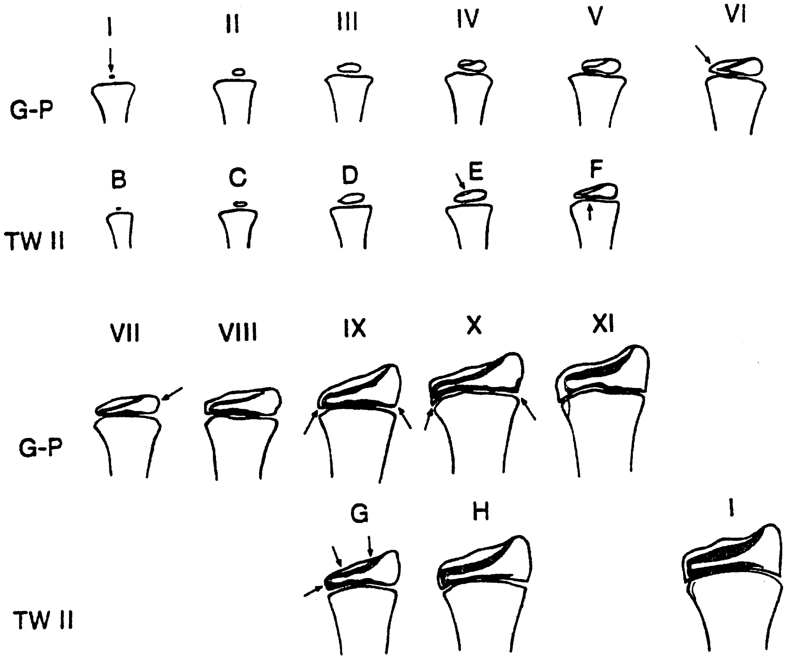

FIGURE 17-2 Maturity indicators for the radius as defined by Greulich and Pyle[5] and Tanner et al.[9]

Maturity indicators must, however, conform to certain prerequisites if they are to be useful. They must possess the quality of "universality," in that they must be present in all normal children of both sexes and they must appear sequentially, and in the same sequence, in all children. In addition, they ought to reflect a continuous process of maturation rather than a discontinuous process. While such criteria may appear obvious, it is possible to find examples of maturity indicators that simply do not conform to these desiderata.

For instance, a recent paper in a clinical journal described "age at semenarche," in terms of a mean and standard deviation, for a sample of boys from the Transkei region of South Africa, who completed a self-administered questionnaire.[23] The question each boy responded to was, "How old were you when you had your first wet dream (ejaculation)?" One can appreciate that the accuracy of the response to such a question is at best dubious, and indeed the authors maintained that their estimate of mean age at semenarche, "was crude, and relied on recall of a fairly nebulous isolated event that in most cases is difficult to recall precisely" (Buga, 1996, personal communication). Such estimates ignore the fundamental rationale of maturity indicators and are not constructive to the accurate determination of sexual maturity.

Without maturity indicators, we cannot develop methods to assess the process and so, when we search for new methods, the "holy grail" of that search is the identification of appropriate indicators of maturity.

Maturational Variation

Maturational variation covers two aspects: the variation of maturation *within* a process and the variation of maturation *between* processes. The former aspect may be observed within sexual maturation from the data reported by Marshall and Tanner[2,3] on British children. They illustrated variation by investigating the percentage of girls or boys within any particular stage of development of one indicator of maturation when they entered a particular stage of another indicator. For instance, 84% of girls were in at least stage 2 of breast development when they entered stage 2 of pubic hair development. In other words, they did not enter pubertal maturation in both breast and pubic hair development simultaneously. Breast development for the vast majority was the first stage of puberty followed by pubic hair development. Similarly, 39% of girls were already adult for breast development when they became adult for pubic hair development.

A similar pattern of variation was observed in males with 99% of boys starting genitalia development prior to pubic hair development. This variation is critical in that it requires any modification of the method to allow for intraindividual variation. Within clinical situations, for instance, the difficulties in accurately rating the various stages of breast, genitalia, or pubic hair development within the Tanner five-point classification, have led to the combination of the stages into a three or four-point "pubertal" staging technique. In the three-point technique, stage P1 represents the prepubertal state (B1/G1; PH1) and stage P3 the postpubertal state (B5/G5; PH5). All indicators of maturational change between these two extremes have been combined into the P2 stage. Therefore, variations within individuals between the different aspects of secondary sexual development are impossible to quantify, and in terms of research to investigate variability in maturation, the pubertal staging technique loses significant sensitivity. The variation of maturation between different aspects of maturity presents difficulties in implying a general maturational level to the individual. Entry into the early stages of puberty is not, for instance, associated with any particular level of skeletal maturity except in the broadest sense. The only real exception to this rule, with regard to skeletal and sexual maturation, is menarcheal age in which skeletal age and chronological age are associated at a level of 0.35 and in which menarche tends to occur at a skeletal age of 12.5–14.0 "years" regardless of chronological age.

Maturity indicators derived from mathematical functions that describe the growth curve might be far more useful than morphological indicators, because much closer associations are evident between markers of somatic growth and skeletal maturity. For instance, skeletal and chronological ages are known to be uncorrelated at 95% of mature height, and therefore skeletal age is more or less fixed at 95% mature height regardless of chronological age. Thus, function parameters that have a real biological meaning have the potential to be appropriate maturity indicators. The problem is that most existing functions resulted from attempts to smooth the growth curve or reduce data rather than understand the biology of growth. For example, the family of models proposed by Preece and Baines[24] (see Chapter 3) resulted from attempts to model the total growth curve with the fewest parameters. Previous attempts by Bock et al.[25] resulted in double or triple logistic curves involving nine or more parameters for which clear biological meanings were not apparent. Preece and Baines[24] were able to model using just five parameters, to which they were also able to assign biological meaning, such as age and height at peak height velocity (PHV). This "biological" meaning resulted from the fact that high correlations were apparent between the function parameter and the maturational event. For example, in Model 1, θ correlated with age at PHV at a 0.99 level for boys and a 0.97 level for girls, $H\theta$ at a 0.99 level with height at PHV in both males and females. But one needs to be cautious about implying direct associations between the function parameters and the maturational events; the rate constants S_0 and S_1, for instance, correlated most strongly with velocity at takeoff and velocity at PHV but only at the 0.50 and 0.55 levels. However, the possibility of using function parameters as maturity indicators is an attractive prospect, particularly as mathematical modeling moves us closer to a more accurate depiction of the pattern of human growth.

Sexual Dimorphism

Ideally any method that assesses maturity should be able to assess the same process of maturation in both males and females. That criterion is true of skeletal and dental maturity assessment methods and also methods that might be developed from mathematical models of the pattern of human growth. It is not, of course, true of all aspects of secondary sexual development, although the gender-specific assessment methods have a great deal in common. In the former methods, sexual dimorphism is accounted for by having gender-specific scores for each bone or tooth and, in the latter, by identifying equivalent functional processes in the different sexes. However, the interpretation of maturation, or the meaning of the attainment of a particular level of maturity, may be different within the sexes. For instance, it could be argued that spermarche and menarche are equivalent stages of maturation in males and females, yet their position within the pattern of growth is quite different and thus their association with other aspects of maturation also differs. Extensive data on menarche demonstrates that it occurs following peak height velocity and toward the latter part of secondary sexual development; that is, in breast stage 3, 4, or 5. Relatively sparse data on spermarche identifies its occurrence at approximately 14 years in boys, which would be in the early or middle part of the adolescent growth spurt and thus indicative of an earlier stage of pubertal maturation.

Maturity and Size

The fact that a large individual is likely to be older and therefore more mature than a small individual was emphasized earlier in this review. This might indicate that size should in some way be included in a consideration of maturation. Indeed, the early methods of skeletal maturity assessment by planimetry used precisely that reasoning. It is now clearly recognized that, except in very general terms, size does not play a part in the assessment of maturation. Size does however enter assessment as a maturity indicator as a ratio measure. For example, the maturity indicator for stage D in the radius of the TWII system is that the epiphysis is “half or more” the width of the metaphysis; that is, the size is relative to another structure within the same area. However, except for such a ratio situation, the only maturity assessment method that uses a quantitative indicator of maturity is testicular volume: 4 ml represents the initiation of pubertal development and 12 ml midpuberty. This is not to say that there is no variation in testicular volume. Like all aspects of growth and development, variability is an inherent aspect of testicular growth. Clinicians, however, use these measures as indicators of normal testicular growth and of the initial and middle stages of pubertal development.

METHODS OF ASSESSMENT

Maturation is assessed using a combination of processes and events. Maturational “processes” include secondary sexual development, dental development, and skeletal development. Maturational “events” include those aspects of maturation that occur once and provide an unambiguous signal that the individual has reached a particular level of maturity. For example, the exact age at which menarche (the first menstrual period) is experienced in girls or the exact the age of peak height velocity during the adolescent growth spurt.

Secondary Sexual Development

Secondary sexual development is assessed using maturity indicators that provide discrete stages of development within the continuous process of maturation. The most widely accepted assessment scale is described as the Tanner Scale or the Tanner Staging Technique. It was developed by Tanner,[26] based on the work of Reynolds and Wines[27] and Nicholson and Harley.[12] Tanner[26] divided the processes of breast development in girls, genitalia development in boys, and pubic hair development in both sexes into five stages and axillary hair development in both sexes into three stages. The usual terminology is to describe breast development in stages B1–B5, genitalia development in stages G1–G5, pubic hair development in stages PH1–PH5 and axillary hair development in stages Al–A3.

Stages of Breast Development (Figure 17-3)

1. Preadolescent: Elevation of papilla only.
2. Breast bud stage: Elevation of breast and papilla as small mound. Enlargement of areolar diameter.
3. Further enlargement and elevation of breast and areola, with no separation of their contours.
4. Projection of areola and papilla to form a secondary mound above the level of the breast.
5. Mature stage: projection of papilla only, due to recession of the areola to the general contour of the breast.

Stages of Genitalia Development (Figure 17-4)

1. Preadolescent: Testes, scrotum, and penis are of about the same size and proportion as in early childhood.
2. Enlargement of scrotum and testes: The skin of the scrotum reddens and changes in texture. There is little or no enlargement of penis at this stage.
3. Enlargement of penis: This occurs first mainly in length. Further growth of testes and scrotum.
4. Increased size of the penis with growth in breadth and development of glans. Further enlargement of testes and scrotum; increased darkening of scrotal skin.
5. Genitalia adult in size and shape.

Stages of Pubic Hair Development (Figure 17-5)

1. Preadolescent: The vellus over the pubes is not further developed than that over the abdominal wall; that is, no pubic hair.
2. Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, appearing chiefly at the base of the penis or along the labia.
3. Considerably darker, coarser, and more curled hair. The hair spreads sparsely over the junction of the pubes.

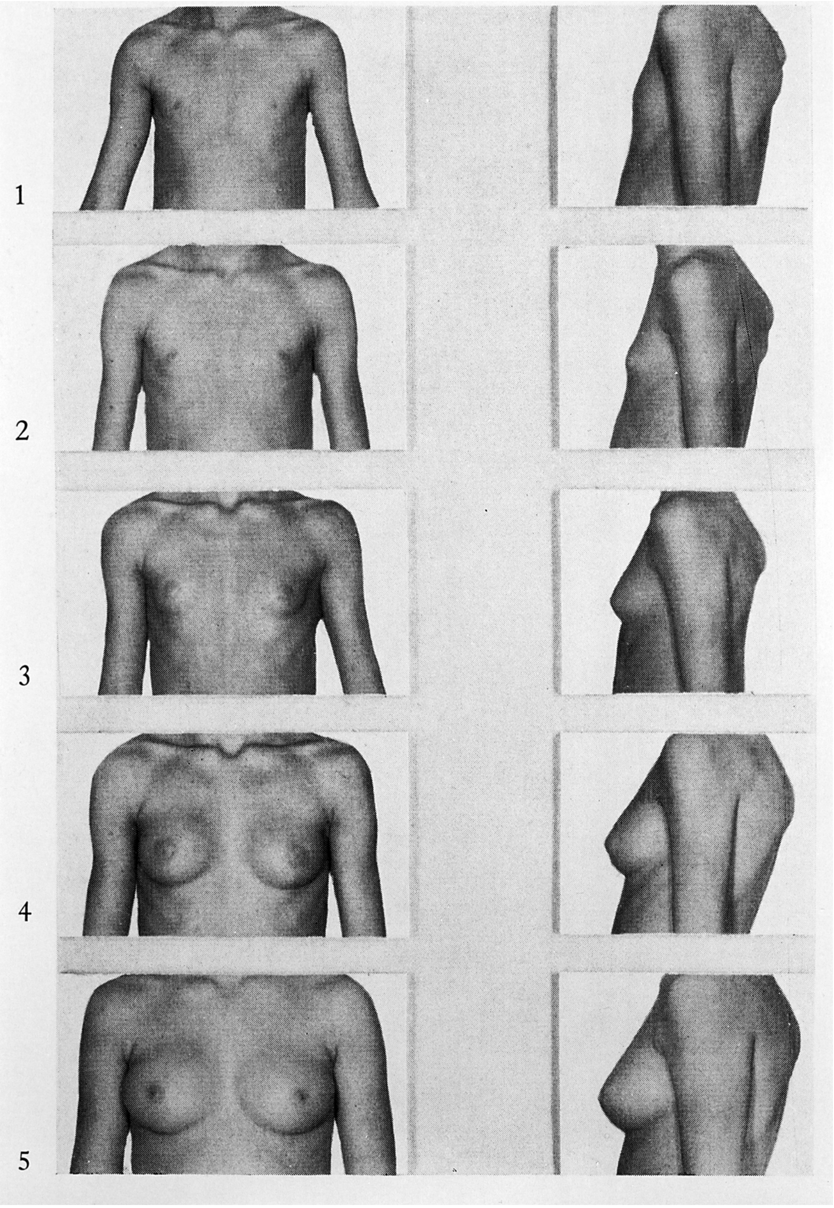

FIGURE 17-3 Breast standards from the Tanner method. (Source: Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

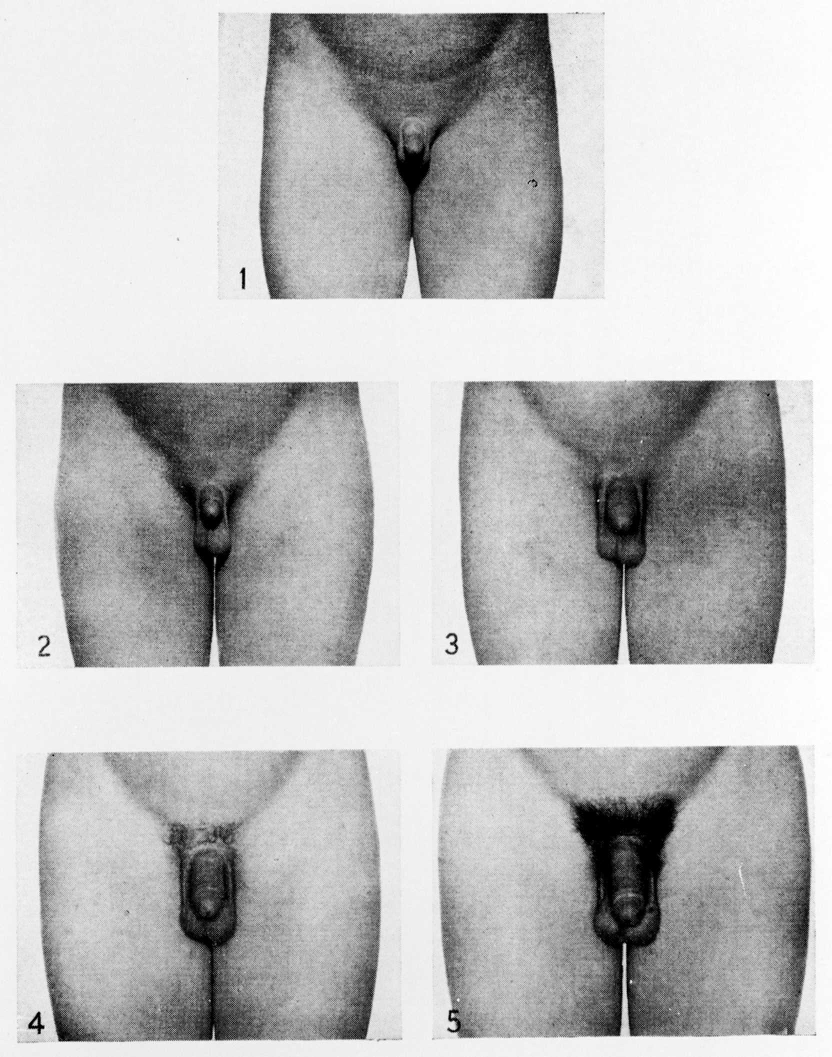

FIGURE 17-4 Genitalia standards from the Tanner method. (Source: Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

4. Hair now resembles adult in type, but the area covered by it is still considerably smaller than in the adult. No spread to the medial surface of the thighs.
5. Adult in quantity and type of hair with distribution of the horizontal or classically feminine pattern. Spread to the medial surface of the thighs but not up the linea alba or elsewhere above the base of the inverse triangle.

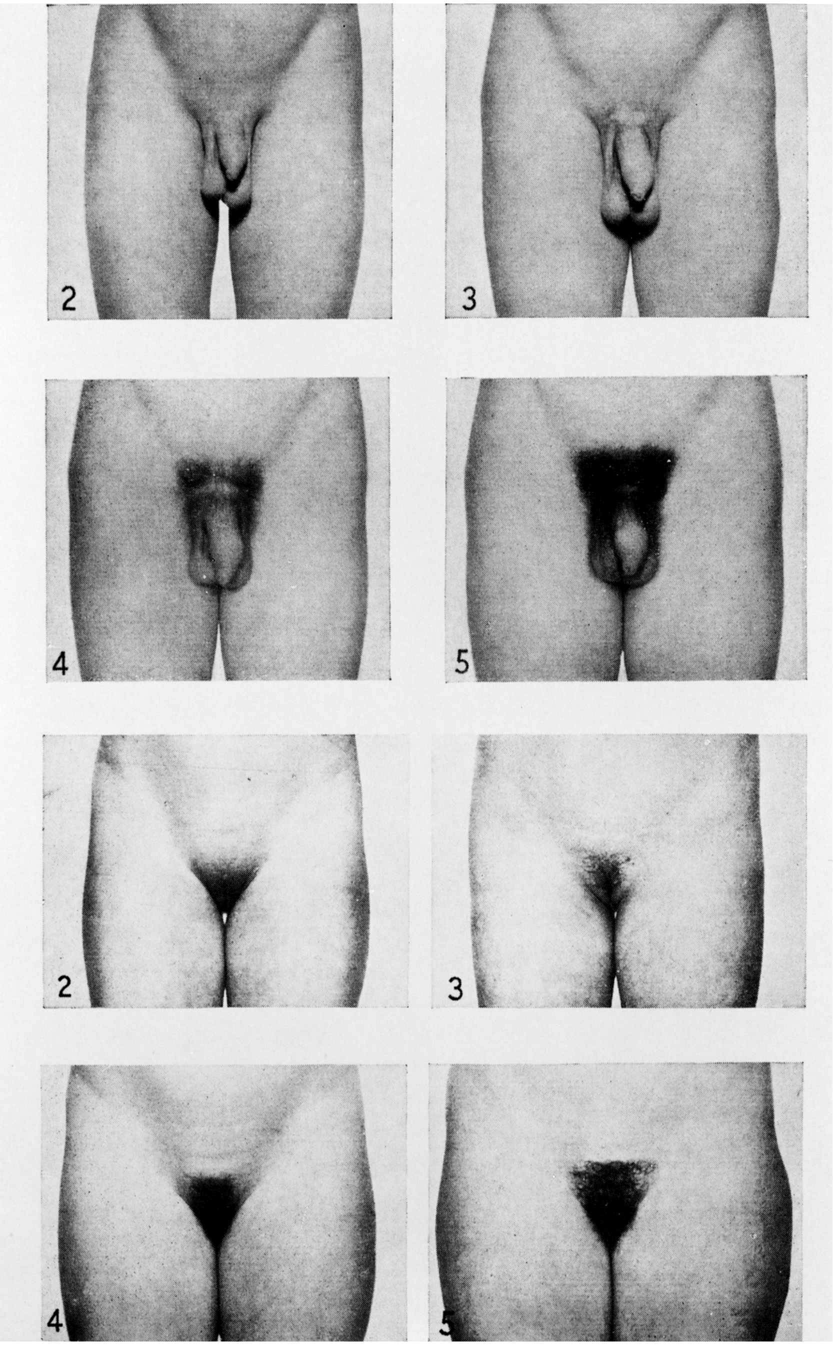

FIGURE 17-5 Pubic hair standards from the Tanner method. (Source: Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.)

Clinical Evaluations

The assessment of secondary sexual development is a standard clinical procedure, and at such times, the full Tanner Scale is used. There are some practical problems with the Tanner stages, however, in that the unequivocal observation of each stage often depends on having longitudinal observations. In most situations, outside the clinical setting, the observations are cross-sectional. This practical difficulty has led to the amalgamation of some of the stages to create pubertal stages. These pubertal stages are either on a three- or four-point scale and combine breast or genitalia development with pubic hair development.[28,29] Assessing breast or genitalia development with pubic hair development is obviously much easier than assessing these maturity indicators separately, but inevitably leads to a lack of sensitivity in the interpretation of the timing and duration of the different stages of pubertal development. Indeed the intrasubject variation in the synchronous appearance of pubic hair and breast or genitalia stages, illustrated in British children by Marshall and Tanner,[2,3] suggests that it may be misleading to expect stage synchronization in as many as 50% of normal children.

Self-Assessment of Pubertal Status

The assessment of secondary sexual characteristics is, to some extent, an invasive procedure, in that it invades the privacy of the child or adolescent involved. Therefore, such assessments on normal children who participate in growth studies, as opposed to those being clinically assessed, are problematical from both ethical and subject compliance viewpoints. To overcome this problem the procedure of “self-assessment” has been developed and validated in a number of studies.

The self-assessment procedure requires the child to enter a well-lit cubicle or other area of privacy, in which are provided pictorial representations of the Tanner Scales and suitably positioned mirrors on the wall(s). The pictures may be either in photographic or line drawing styles as long as the contents are clear. To each picture of each stage is appended an explanation, in the language of the participant, of what the stage represents. The participant is instructed to remove whatever clothing is necessary to be able to properly observe their pubic hair and genitalia or pubic hair and breast development in the mirrors. The participant then marks on a separate sheet his or her stage of development and seals that sheet within an envelope on which is marked the study identity number of the participant. The envelope is either left in the cubicle or handed to the observer on leaving the cubicle.

The results of validation studies vary greatly, depending on the age of the participants (e.g., early or late adolescence),[30] gender,[31,32] the setting in which assessments are performed (e.g., school or clinic),[32,33] ethnicity,[34] and whether the subjects are part of a distinct diagnostic group, such as cystic fibrosis,[35] anorexia nervosa,[36] or the socially disadvantaged.[37] Younger, less-developed children tend to overestimate their development, and older more-developed children tend to underestimate. Boys have been found to overestimate their development while girls have been more consistent with experts.[31]

The amount of attention given to explaining the required procedure appears to be of major importance. Thus, excellent rating agreement between physicians and adolescents have been found in clinical settings, with kappa coefficients between 0.66 and 0.91,[33,38,39] but rather less agreement in school settings (kappa = 0.35–0.42; correlations = 0.25–0.52).[32,33] Improved agreement in clinical settings probably reflects the more controlled environment of a physician's surgery as opposed to a school. The main reason for low correlations, and thus poor validity, in any setting with any group of participants is likely to be centered around the amount of explanation provided the child. When the participant has been the subject of a clinical trial and the scientist or clinician spent considerable time and effort ensuring that the child is completely appraised of what he or she has to do, then validity is high. Less effort in explaining procedures leads to lower validity.

The procedure that should be adopted is that the observer explain the procedure thoroughly to the participant using appropriate (nonscientific) language and invite questions to ensure that the participant fully understands the procedure. Only when the observer is sure that understanding is total should the child be allowed to follow the procedure. Randomized reliability assessments by the observer would, of course, be ideal but also ethically difficult to substantiate.

Dental Development

Dental development is best assessed by taking panoramic radiographs of the mandible and maxilla and scoring the stages of formation and calcification of each tooth using the method developed by Demirjian, Goldstein, and Tanner[11] and Demirjian and Goldstein.[40] Scores are assigned to the stages of development of the seven mandibular teeth on the left side (there are no significant between-side differences) and these lead to a dental maturity score comparable to the skeletal maturity scores resulting from the Tanner-Whitehouse (TW) skeletal maturity technique described here. This score can be translated into the dental age. A similar system is available for sets of four teeth, seen on apical radiographs, notably M1, M2, PM1, PM2 or alternatively I1, M2, PM1, PM2.

Concern over the exposure of normal children to radiation has resulted in tooth emergence as the most commonly used method to obtain estimates of dental maturity. The emergence of the teeth above the level of the gum is recorded either by oral inspection or in a dental impression. Most observers have considered that a tooth has emerged if any part has pierced the gum, but some have used the criterion of the tooth being halfway between gum and final position.[41] Three types of standards have been developed that give either the number of teeth emerged at specific ages; the average age when 1, 2, 3, and so forth teeth have emerged; or the median age in a population for the emergence of a specific tooth or pair of teeth. The latter technique is considered the best for permanent teeth because of the individual variation in the order of emergence of each tooth pair.[41]

Skeletal Development

Although a number of techniques exist to assess skeletal maturity assessment, procedures have been dominated by two different approaches to the problem: the "atlas" technique of Greulich and Pyle[5] and the Tanner-Whitehouse "bone-specific scoring" technique.[10] Both use the left hand and wrist to estimate a skeletal age or bone age yet they are different both in concept and in method. Greulich-Pyle bone ages are most commonly assessed by comparing a radiograph to a series of standard radiographs photographically reproduced in the atlas. The chronological age assigned to the standard most closely approximating the radiograph is the bone age of the subject. In practice, a more precise estimate of bone age may be obtained by assessing each bone in the hand and wrist separately, but this is rarely done. So, there are errors in most Greulich-Pyle estimations, because the dysmaturity in the hand and wrist is not acknowledged. The system is based on subjects from Cleveland, Ohio, who were assessed during the 1920s and 1930s. The Tanner-Whitehouse system requires 20 bones of the hand and wrist to be assessed individually and a score to be assigned to each. The summation of the scores results in a bone maturity score, which is equivalent to a particular bone age. This technique used subjects from a variety of studies conducted in the south of England during the 1950s and 1960s. Although the latter is more recent, the effect of positive secular trends and population differences in average maturity status means that estimates of skeletal age based on either technique must be viewed with some caution. However, the statistical rationale of the bone-specific scoring technique can be applied to any series of radiographs from a representative sample of a population. In contrast to the atlas technique it is thus possible to develop specific national references for the assessment of skeletal maturity using a bone-specific approach that would result in a more sensitive clinical appraisal.

Age at Menarche

Age at menarche is usually obtained in one of three ways: status quo, retrospectively, or prospectively. Status quo techniques require the girls to respond to the question, "Do you have menstrual cycles (periods)?" The resulting data on a sample of girls produces a classical dose-response sigmoid curve that may be used to graphically define an average age at menarche. More commonly, the data are analyzed using logit or probit analysis to determine the mean or median age at menarche and the parameters of the distribution, such as the standard error of the mean or the standard deviation. Retrospective techniques require the participants to respond to the question, "When did you have your first period?" Most adolescents can remember to within a month, and some to the day, when this event occurred. Others may be prompted to remember by reference to whether the event occurred during summer or winter, whether the girl was at school or on holiday, and so on. One interesting result of such retrospective analyses is that there appears to be a negative association between the age of the women being asked and the age at which they report menarche—the older are the women, the younger they believe they were. Such results have been found in both developed and developing countries and cast a seed of doubt about the reliability of retrospective methods beyond the teenage and early adult years. Prospective methods are normally only used in longitudinal monitoring situations, such as repeated clinic visits or longitudinal research studies. This method requires the teenager to be seen at regular intervals (usually every 3 months) and be asked on each occasion whether or not she has started her periods. As soon as the response is positive an actual date on which menarche occurred can be easily obtained.

There is little doubt that the prospective method is the most accurate in estimating menarcheal age, but it has the disadvantage of requiring repeated contact with the subjects. That is seldom possible except in clinical situations, and it is thus more likely that status quo and retrospective methods are the technique of choice. Status quo techniques that rely on logit or probit analysis require large sample sizes because the analysis requires the data to be grouped according to age classes. With few subjects, broader age ranges are required, such as whole or half years, with a consequent loss of precision in the mean or median value. Retrospective methods result in parametric descriptive statistics but have the problem of the accuracy of recalled ages at this particular event.

Secondary Sexual Events in Boys

While status quo, prospective, and retrospective methods may easily obtain age at menarche, assessments of secondary sexual development in boys are complicated by the lack of a similar clearly discernible maturational event. Attempts to obtain information on the age at which the voice breaks or on spermarche are complicated by the time taken for the voice to be consistently in a lower register and the logistical complications involved in the assessment of spermarche. Testicular volume, using the Prader orchidometer,[42] is commonly the only measure of male secondary sexual development outside the rating scales previously mentioned, although other measurement techniques have been described to estimate testicular volume.[43]

The detection of spermatozoa in the urine has been proposed as a quick, noninvasive method to assess the functional state of the maturing gonad and may be useful as a screening technique in population studies.[44–49] Its use, however, may be limited because longitudinal[48,50] and cross-sectional[47] studies have shown that spermaturia is a discontinuous phenomenon.

Landmarks on the Growth Curve

The identification of landmarks on the human growth curve that can be used for comparison between individuals or groups started with age at peak height velocity. This is the most distinctive feature of the velocity curve during adolescent growth and may be determined in individual longitudinal data as a change in acceleration from positive to negative values. Use of other landmarks on the curve, such as ages at takeoff and at the cessation of growth and the magnitude of height or weight velocity at these ages, did not become prevalent until the implementation of mathematical curve-fitting techniques became possible using personal-computer-based software. Initial curve-fitting techniques used only part of the growth curve (e.g., from birth to the start of adolescence) or involved the addition of different functions. The major problem with these early techniques, apart from their mathematical complexity and biological interpretation, was their relative inability to cover the transition between developmental periods such as preadolescence to adolescence. This was solved to a certain extent by the development of single curves that described growth from birth to adulthood.[24,25] However, long-term parametric models have the advantage that the researchers preselect the shape of the resulting growth curve. The choice of the model necessitates the acceptance of its form as representative of the pattern of growth. Individuals or samples departing from the standard pattern of growth in height or weight would not be fitted well by any of these parametric functions. Estimates of landmarks on the growth curve are difficult to determine. Tanner and Davies,[51] for instance, when developing the clinical longitudinal standards for American children, relied on empirically derived values for the magnitude of peak velocity because "parametric curves . . . are insufficiently flexible to accommodate the full rise of the observed curves" during adolescence (p. 328). The widely used Preece-Baines curve,[24] for example, is known to underestimate the peak velocity.

Nonparametric models, such as the smoothing spline function[52] and kernel estimation,[53,54] have been proposed to overcome the problems inherent in preselection of a pattern of growth. Nonparametric techniques are usually short-term functions that smooth adjacent data points rather than fit a function to data from birth to adulthood. They have been useful in demonstrating the sensitivity of growth analysis using acceleration[53,54] but cannot result in mathematically derived values for adolescent landmarks such as the age and magnitude of peak velocity. Such landmarks, if taken from curves that have been smoothed using nonparametric techniques, may be more accurately determined than if derived from a parametric function. However, that accuracy depends on the frequency of data points during the period of adolescence. The inability of preselected parametric functions to fit abnormal growth and the retrospective nature of growth assessment of nonparametric methods make these techniques useful as research tools but not for diagnosis and monitoring the value of treatment.

REFERENCES

1. Bogin B. Patterns of Human Growth. Cambridge: Cambridge University Press, 1988.
2. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291–303.
3. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13–23.

4. Acheson RM. Maturation of the skeleton. In: Falkner F (ed). Human Development. Philadelphia: Saunders, 1966:465–502.
5. Greulich WW, Pyle S.I. Radiographic Atlas of the Skeletal Development of the Hand and Wrist. Palo Alto, CA: Stanford University Press, 1959.
6. Acheson RM. A method of assessing skeletal maturity from radiographs. J Anat (Lond). 1954;88:498–508.
7. Acheson RM. The Oxford method of assessing skeletal maturity. Clin Orthop. 1957;10:19–39.
8. Tanner LM, Whitehouse RH. Standards for Skeletal Maturity. Part I. Paris: International Children's Centre, 1959.
9. Tanner JM, Whitehouse RH, Healy MJR. A New System for Estimating the Maturity of the Hand and Wrist, with Standards Derived from 2600 Healthy British Children. Part II. The Scoring System. Paris: International Children's Centre, 1962.
10. Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H. Assessment of Skeletal Maturity and Prediction of Adult Height, 2nd ed. London: Academic Press, 1983.
11. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol. 1973;45:211–227.
12. Nicholson AB, Harley C. Indices of physiological maturity. Child Develop. 1952;24:3–38.
13. Meindl RS, Lovejoy CO. Ectocranial suture closure: A revised method for the determination of skeletal age at death and blind tests of its accuracy. Amer J Phys Anthropol. 1985;68:57–66.
14. Todd TW. Atlas of Skeletal Maturation. Part I, The Hand. St. Louis: Mosby, 1937.
15. Hellman M. Ossification of epiphyseal cartilages in the hand. Amer J Phys Anthropol. 1928; 11:223–257.
16. Rotch TM. A study of the development of the bones in childhood by the roentgen method, with the view of establishing a developmental index for the grading of and the protection of early life. Trans Amer Assn Physicians. 1909;24:603–630.
17. Bardeen CR. The relation of ossification to physiological development. J Radiol. 1921;2:1–8.
18. Sontag LW, Lipford J. The effect of illness and other factors on appearance pattern of skeletal epiphyses. J Pediat. 1943;23:391–409.
19. Lowell F, Woodrow H. Some data on anatomical age and its relation to intelligence. Pedagog Semin. 1922;29:1–15.
20. Carter TM. Technique and devices in radiographic study of the wrist bones of children. J Educ Psychol. 1926;17:237–247.
21. Flory CD. Osseous development in the hand as an index of skeletal development. Monogr Soc Res Child Develop. 1936;1:3.
22. Pryor JW. The hereditary nature of variation in the ossification of bones. Anat Rec. 1907;1:84–88.
23. Buga GAR, Amoko DHA, Ncayiyana DJ. Sexual behaviour, contraceptive practice and reproductive health among school adolescents in rural Transkei. S Afr Med J. 1996;86:523–527.
24. Preece MA, Baines MI. A new family of mathematical models describing the human growth curve. Ann Hum Biol. 1978;5:1–24.
25. Bock RD, Wainer H, Peterson A, Thissen LM, Roche A. A parameterization for individual human growth curves. Hum Biol. 1973;45:63–80.
26. Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.
27. Reynolds EL, Wines JV. Physical changes associated with adolescence in boys. Amer J Dis Child. 1948;75:329–350.
28. Kulin BE, Bwibo N, Mutie D, Santner SJ. The effect of chronic childhood malnutrition on pubertal growth and development. Amer J Clin Nutrit. 1982;36:527–536.
29. Chaning-Pearce SM, Solomon L. A longitudinal study of height and weight in black and white Johannesburg children. S Afr Med J. 1986;70:743–746.
30. Varona-Lopez W, Guillemot M, Spyckerelle Y, Deschamps JP. Self assessment of the stages of sex maturation in male adolescents. Pediatrie. 1988;43:245–249.
31. Sarni P, de Toni T, Gastaldi R. Validity of self-assessment of pubertal maturation in early adolescents. Minerva Pediat. 1993;45:397–400.

32. Wu WH, Lee CH, Wu CL. Self-assessment and physician's assessment of sexual maturation in adolescents in Taipei. Chung Hua Min Kuo Hsiao ErhKo I Hsueh Hui Tsa Chih. 1993;34:125–131.
33. Schlossberger NM, Turner RA, Irwin CE, Jr. Validity of self-report of pubertal maturation in early adolescents. J Adoles Health. 1992;13:109–113.
34. Hergenroeder AC, Hill RB, Wong WW, Sangi-Haghpeykar H, Taylor W. Validity of self-assessment of pubertal maturation in African American and European American adolescents. J Adoles Health. 1999;24:201–205.
35. Boas SR, Falsetti D, Murphy TD, Orenstein DM. Validity of self-assessment of sexual maturation in adolescent male patients with cystic fibrosis. J Adoles Health. 1995;17:42–45.
36. Hick KM, Kutzman DK. Self-assessment of sexual maturation in adolescent females with anorexia nervosa. J Adoles Health. 1999;24:206–211.
37. Hardoff D, Tamir A. Self-assessment of pubertal maturation in socially disadvantaged learning-disabled adolescents. J Adoles Health. 1993;14:398–400.
38. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. Pediat. 1980; 66:918–920.
39. Brooks-Gunn J, Warren MP, Russo J, Gargiulo J. Validity of self-report measures of girls' pubertal status. Child Dev. 1987;58:829–841.
40. Demirjian A, Goldstein H. New systems of dental maturity based on seven and four teeth. Ann Hum Biol. 1976;3:411– 421.
41. Eveleth PB, Tanner JM. Worldwide Variations in Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1990.
42. Prader A. Testicular size: Assessment and clinical importance. Triangle. 1966;7:240.
43. Daniel WA, Feinstein RA, Howard-Pebbles P, Baxley WD. Testicular volume of adolescents. J Pediatr. 1982;101:1010–1012.
44. Schaefer F, Marr J, Seidel C, Tilgen W, Scharer K. Assessment of gonadal maturation by evaluation of spermaturia. Arch Dis Child. 1990;65:1205–1207.
45. Baldwin B. The determination of sex maturation in boys by a laboratory method. J Comp Psychol. 1928;8:39–43.
46. Richardson D, Short R. Time of onset of sperm production in boys. J Biosoc Sci. 1978;5(Suppl): 1525.
47. Hirsch M, Shemesh J, Modan M. Emission of spermatozoa: Age of onset. Int J Androl. 1979; 2:289–298.
48. Nielson CT, Skakkebaek NS, Richardson DW. Onset of the release of spermatozoa (spermarche) in boys in relation to age, testicular growth, pubic hair, and height. J Clin Endocrinol Metab. 1986;62:532–535.
49. Kulin HE, Frontera ME, Demers LD, Bartholomew MJ, Lloyd TA. The onset of sperm production in pubertal boys. Amer J Dis Child. 1989;143:190–193.
50. Hirsch M, Lunenfeld B, Modan M, Oradia J, Shemesh J. Spermarche—The age of onset of sperm emission. J Adoles Health Care. 1985;6:35–39.
51. Tanner JM, Davies PSW. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985;l07:317–329.
52. Largo RH, Gasser TH, Prader A, Stuetzle W, Huber PJ. Analysis of the human growth spurt using smoothing spline functions. Ann Hum Biol. 1978;5:421–434.
53. Gasser T, Kohler W, MulIer HG, Kneip A, Largo R, Molinari L, et al. Velocity and acceleration of height growth using kernel estimation. Ann Hum Biol. 1984;11:397–411.
54. Gasser T, Kohler W, Muller HG, Largo R, Molinari L, Prader A. Human height growth: Correlational and multivariate structure of velocity and acceleration. Ann Hum Biol. 1985;12:501–515.

18

GROWTH REFERENCES AND STANDARDS

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INTRODUCTION

Purpose

Growth assessment is comparison. To measure the height of an individual we use an accurately calibrated instrument called a *ruler*. We assess the height status of an individual in just the same way, with a form of calibrated instrument called a *growth reference*. Without some form of reference, growth assessment is arbitrary and unsatisfactory.

But there is an important difference between measuring a child's height and assessing his or her growth status. On the whole, rulers agree about how long a meter is, but an individual's growth rate depends on a wide variety of factors, including sex, age, pubertal stage, parental size, ethnicity, health, and socioeconomic status. The ruler to assess it needs to be multidimensional to take all the relevant factors into account. This is the role of the growth reference, to provide a way of displaying expected growth as a function of (some of) these other factors in a compact, accessible, and visually appealing form.

Growth and Size

It is important to be clear about the distinction between growth, on the one hand, and size, on the other. Strictly speaking, growth is a form of *velocity*, the rate of change in size over time, and it requires measurements on at least two occasions to assess it. The term *growth chart* is unfortunate, as most such charts do not assess growth at all, they measure size. Tanner proposed that, by analogy with growth and velocity, charts measuring size should be called *distance* charts—they measure the *distance* the child traveled on the journey from conception to adulthood. As we shall see later, most distance charts not only fail to assess growth, but their underlying reference data also lack any information about growth. Nevertheless this chapter follows common practice by referring to size or distance charts as growth charts where necessary.

Chart Form

A growth reference is essentially a database defining the statistical distribution of one or more measures of size or growth, indexed by sex, age and/or other factors. The information may be summarized in a table but for clinical purposes is usually presented as a chart plotted against age. This form of presentation has developed over the last hundred years or so.[1] An important principle of growth charts is that the curves making up the chart should appear smooth.

The frequency distribution of each measurement can be summarized in several ways. At its simplest, the mean and standard deviation (SD) are tabulated by age and sex. Then, assuming a normal or Gaussian distribution, the mean and SD define the entire distribution and its centiles (see later).

Curves are drawn on the chart to represent the distribution at each age. A common pattern is to draw seven curves, corresponding to the mean, one SD above and below the mean, then two SDs and three SDs similarly. So, seven curves are spaced one SD apart, the pattern used for the World Health Organization (WHO)/U.S. Centers for Disease Control (CDC)/National Center for Health Statistics (NCHS) international growth reference.[2] The British 1990 reference[3] uses a format based on nine curves, spaced two thirds of an SD apart. This spacing gives a set of curves very similar to the centile-based curves described later, but with a greater distributional range.[4] With a normal distribution, SD-based curves appear as equally spaced on the chart at each age.

When the distribution is not normal, so that the mean and SD are insufficient by themselves to define it, the frequency distribution can be specified in terms of empirical centiles. A centile is a point on the distribution that splits the population into two specified fractions. The 50th centile, also known as the median, is the midpoint of the distribution, with 50% to the left of it and 50% to the right. The third centile has 3% to the left of it and 97% to the right. For nonnormal data, centiles are estimated directly from the data (empirical centiles), whereas with normal data, the centiles are calculated from the mean and SD. The latter approach is more efficient, as the mean and SD are estimated more precisely than individual centiles.

A set of several centiles is used in the growth chart to represent the range of the distribution, the values chosen to be symmetric about the median. A common set is the seven centiles 3rd, 10th, 25th, 50th, 75th, 90th, and 97th, approximately two thirds of an SD apart for a normal distribution. For comparison the nine-centile set for the British 1990 reference, based on an exact two thirds SD spacing, is the 0.4th, 2nd, 9th, 25th, 50th, 75th, 91st, 98th, and 99.6th, with the middle seven centiles very similar. Other sets may include three or five centiles. Cole[4] discussed the reasons why particular centile sets are used.

A centile *curve* is a curve joining the values of a specified centile at different ages. So the percentage chance of an individual child's value lying below a given centile curve is given by the value of the centile; for example, a 3% chance below the third centile curve. In addition, this chance is the same at all ages, assuming that the child comes from the reference population on which the chart is based.

Assessment

The curves on the chart represent either centiles or fractions of an SD above or below the mean. The assessment of individual subjects follows the same principle. The subject's measurement is plotted on the chart and the corresponding centile or SD relative to the mean is read off it. Take a girl 3 years old who is 90 cm tall—her height is on the 11th centile of the British reference, just above the 9th centile on the chart, and it corresponds to 1.25 SDs below the mean. By convention, the child's SD position on the chart is known as the SD score (SDS) or *z*-score for short.

Much debate concerns the pros and cons of centiles and SD scores for assessing growth. Centiles are on a scale from 1 to 99, centered on 50 (0 and 100 are offscale), and they correspond to the percentage chance of a reference child having a smaller value than the subject. The SD score scale is centered on 0, with an SD of 1, and is normally distributed.

Centiles are easier for subjects and their parents to understand, whereas SD scores are preferred by researchers, as they are better behaved statistically. In addition, they provide greater resolution than centiles in the tails of the distribution. The international growth reference, for example, uses SDs rather than centiles to quantify the size of malnourished individuals who lie well below the third centile. The 3rd, 1st, and 0.1th centiles, for example, correspond to SD scores of –1.9, –2.3, and –3.1, so that the region between the –2 and –3 SD curves on the chart corresponds to a very narrow centile range.

A third form of assessment is "percent of the median," where the measurement is expressed as a percentage of the median value for the child's age and sex. This is used mainly in the developing world to assess nutritional status and is a simpler version of the SD score. An SD score of 0 always corresponds to 100% of the median, yet at the same time an SD score of –2 corresponds to 92% of the median for height and only 80% for weight. The percent of the median does not take into account the variability of the measurement, while the SD score does.

So a child's position on the chart can be expressed as a centile, an SD score, or a percentage of the median. The secondary purpose of the chart is to follow the child over time and see how his or her position changes with growth. Normally, the children stay close to their previous position but they can change position quite dramatically; that is, *cross centiles*, up or down. It is useful to know how much centile crossing to expect, but the distance chart does not contain this information. A velocity chart is needed to assess centile crossing (see later).

Unconditional and Conditional References

Some growth references are called *conditional*, meaning that the reference data are *conditional* on, or adjusted for, some specified factor. Examples are references conditional on growth tempo or mid-parent height. But it is a misleading term, as all growth references are conditional to some extent—on age and sex if nothing else. *Conditional* is taken here to mean conditional on factors over and above age and sex. References for velocity are a particular and important case of conditional references.

Structure of Chapter

The process of developing references consists of four main stages, involving first the choice of the reference population; then the drawing of the sample; then data collection, cleaning, and analysis; and finally the production of the chart. The chapter follows the same structure. Conditional references involve different statistical principles from unconditional references and are discussed separately.

DEFINING THE REFERENCE POPULATION

The choice of reference population is one of the most important decisions to make when developing a growth reference. It relates to how the reference will be used, by whom, and on which subjects. There are two key questions: Is the reference to be used primarily as a clinical or public health tool? And, is it intended to reflect “optimal” or “typical” growth?

Clinical or Public Health Tool

For doctors involved in the care of individual patients, the growth chart is an essential part of their clinical toolkit. The child’s measurement centiles are a direct measure of health, and the medical assessment of the child involves interpreting the centiles. If the child is not representative of the chart’s reference population, the centiles will be biased and the growth assessment may be invalid.

For public health purposes the applicability of the chart to the individual child is less important. The aim is to summarize the nutritional status of a *group* of children, with a view to comparing the group with other groups (e.g., by socioeconomic status), so that the position of the individual child, or indeed the group, on the chart is not the primary concern.

These alternative aims are contradictory. The first requires the chart to be appropriate for the child, while the second applies to different groups of children, and it cannot be appropriate for them all. This fundamental contradiction lies behind many arguments about the use of growth charts. In practice, a compromise is reached where the chart can be useful both clinically and in public health terms—see later.

For clinical use, the chart's reference population needs to be clearly defined in geographical, cultural or social terms. An example is the British 1990 reference,[3] representative of ethnic white children living in England, Scotland, and Wales in 1990. "White" was originally specified because ethnic groups differ in their growth potential. An obvious disadvantage of this definition is that British ethnic minority children are excluded from the reference, which implies that they need ethnic-specific references of their own. But, in practice, there are many different ethnic minorities and the alternatives are compounded by ethnic mixing of the races, so that separate charts for all are quite impractical. The compromise is to use the British chart for everybody, irrespective of ethnic makeup, but to introduce ethnic-specific adjustments where necessary to extend the coverage to ethnic minorities.[5] These adjustments can be estimated on relatively small samples of children, far fewer than needed to derive a full growth chart.

Other examples of charts for clinical use are syndrome-specific charts, such as for children with Down[6] or Turner's syndrome.[7] The growth of such children is known to differ from that of children without the disorder, so the syndrome-specific chart is appropriate. Another example is a chart for breast-fed infants, who grow differently from formula-fed infants. But this is a less clear-cut example, as the mother's decision whether or not to breast feed is not only a social but also a health issue. And this relates to the question of references versus standards—see later.

For public health use, the chart need not be based on any particular group, so long as it politically acceptable. Charts representative of the national population are obviously popular, like the British 1990 chart, but in principle a single chart for the whole world could be just as useful. Unfortunately, politics tends to intrude at this point, and developed countries prefer to use their own charts rather than work toward international comparability. In the developing world, the WHO/NCHS/CDC chart has fulfilled this international role for the last 20 years, and it has been important in providing comparisons of malnutrition prevalence worldwide.

Reference or Standard

In addition to selection by geography or ethnic background, the reference population can be identified on health grounds, excluding children with a growth disorder, for example. The assumption here is that the growth portrayed by the chart is better than for the unselected population and so is to some degree optimal. In this case, the growth reference is known as a growth *standard* rather than a reference. (Growth references based on unselected populations are also often called *standards*, but strictly this is incorrect.)

References based on healthy subgroups (i.e., standards) can be contentious. Three examples are birth weight in premature babies, height in children with Down syndrome, and growth in elite groups in the developing world.

Babies who are induced prematurely tend to be sicker and hence lighter than babies delivering spontaneously at the same gestation. For this reason, some argue that birth-weight standards should exclude premature induced babies. But this ignores the fact that all premature babies are to some extent unhealthy—they are born earlier than they should be. Cole, Freeman, and Preece[8] discussed this in more detail.

Similarly with Down syndrome, up to a third of children are born with cardiac defects that can materially affect their growth. Most defects are now corrected within the first year, but some children remain appreciably growth retarded later in childhood. Again, the case is made to exclude from the reference those with serious cardiac defects.

Children in the developing world of high socioeconomic, or "elite," status are known to grow better than their poorer contemporaries. Indeed, they can grow as well as children in the developed world.[9] This has been the motivation for some developing world countries, such as India, to base their national growth standards on elite children.

Although there are advantages in restricting the reference population on health grounds, there are also disadvantages. First, if the chart is restricted to a healthy subset of children, how, logically, does one assess the growth of those children that have been excluded? By definition, the chart is not appropriate for them, as it portrays growth in children who have been selected to grow better on average.

Against this, elite standards, it is argued, show how the child *might* grow if his or her socioeconomic status were to be raised. The chart documents the *potential* for growth. But this same argument does not apply to induced premature babies or Down syndrome children with cardiac defects, in each case the children's status is immutable and the chart can never be appropriate for them.

The second disadvantage of growth standards is the need to define *health*. Criteria are required to identify which reference subjects to include and which to exclude on health grounds, and this is usually arbitrary. The preceding examples happen to have fairly clear-cut criteria (although the severity of cardiac defect in Down syndrome children needs to be specified), but often this does not hold. For example, should one exclude children with asthma, or renal disease, from the reference population? These conditions affect growth in some children but not others. The case can be made either way, to include or exclude them, but ultimately it is arbitrary.

For growth assessment in the developed world, it is simpler to use a reference than a standard, so that all children are eligible for the reference dataset irrespective of health status. In practice, the proportion of children excluded on health grounds is likely to be small anyway, so that the decision to include or exclude them has little effect on the fitted centiles. This in itself is a strong argument for including everyone.

DRAWING THE SAMPLE

Having settled on the reference population, the next stage is to decide the study design. This involves answering such questions as these: Is the focus of the study growth distance or growth velocity? How big should the sample be? How should the sample be chosen?

Design: Cross Sectional, Longitudinal, Mixed Longitudinal?

The most common form of growth study is the cross-sectional survey. This collects data on children over a range of ages, each child contributing a measurement at a single moment in time. Such a design is conventionally called a *growth survey*, but it contains no information about growth as each child is seen only once.

To assess growth, the survey needs to measure subjects more than once. Where all subjects are measured repeatedly, this is a longitudinal design, while if only some of the subjects are measured again this is a mixed longitudinal design. Longitudinal designs are more costly than cross-sectional designs for several reasons: They last longer, they have to maintain subject contact, and often it is cheaper to keep highly trained staff employed than to recruit new staff at each measurement occasion.

Longitudinal designs provide information not only on mean growth but also, and more important, on the variability of growth. Cross-sectional designs can estimate, say, the mean annual growth rate through the difference in size of successive year groups, but they provide no information about the variability of growth.

The main difference between a longitudinal and a mixed longitudinal design is the time period over which growth is assessed. Longitudinal designs cover longer periods. If annual velocities are the only concern, then two successive cross-sectional surveys 1 year apart, with say 50% of subjects measured on both occasions, is a mixed longitudinal design that provides all the required growth velocity information. Tanner[10] discussed this design in some detail and highlighted its statistical efficiency.

Longitudinal designs, with infants recruited at or before birth and followed for extended periods, have been popular in the past but less so now. See, for example, the coordinated studies carried out in London, France, Switzerland, and elsewhere.[11] Their main advantage is that they provide complete growth curves for individual children, which cannot be obtained in any other way. But longitudinal designs are expensive, for the reasons described already, and mixed designs have tended to take their place.

The age range of the data is another important aspect of the design. Should it start at birth? If so, should it include some premature births? Should it extend to adulthood? When *is* adulthood—18, 20, 25 years old? The answers to these questions may relate to the ease or difficulty of obtaining the sample at particular ages, and there are statistical arguments for and against different age ranges. These issues need to be considered and agreed on at the outset.

Sample Size

The estimation of sample size through a power calculation is standard practice in medical research, yet it is surprisingly difficult to apply to growth studies. Traditional sizes of study have developed over the years, but they are difficult to justify statistically. The problem is often that the data can be used to estimate both distance and velocity, and it is not clear which should determine the sample size.

A common rule of thumb is a sample containing 200–300 subjects per age group. This is, broadly speaking, the size of the European longitudinal growth studies of the 1950s and 1960s, with larger numbers recruited and rather smaller final sample sizes. Yet the number is hard to justify statistically. In addition, it is not helpful in a cross-sectional study: What is the width of the age group—1 month, 3 months, 1 year, or what?

The WHO Multicentre Growth Reference Study[12] used the criterion of 200 subjects per 3-month age-sex group for a longitudinal design from birth to 2 years (i.e., 200 subjects per sex altogether) and a similar cross-sectional design over the age range 18 months–6 years, giving a sample size of 800 per year. Extrapolated to 0–20 years this implies a sample of 16,000 subjects per sex, which is very substantial. In practice, many surveys are appreciably smaller, even down to one 10th the size. So what is lost when the smaller sample sizes are used?

Put simply, the loss is in the resolution. The information needed to construct a growth reference distance curve is the mean and standard deviation at each age, possibly plus information about the shape of the distribution—see later. Empirical evidence from fitting growth centiles to surveys of different sizes suggests that a survey of, say, 2000, or 50 per year per sex from 0–20 years, estimates the mean well and the standard deviation moderately well but provides little information about the distribution. Conversely a survey of 16,000 provides ample information on all three. This provides a "ball park" figure for the sample size.

Weighting by Age or Extending Age Range

The precision with which the curve is estimated varies with age—it is highest in the middle and lowest at the extremes, due to the presence of "edge effects." To compensate for edge effects, two strategies are available: One is to oversample at the extremes, with say 2–3 times as many subjects in the extreme age groups compared to other ages; the other is to extend the age range. The latter approach is not available at birth, but at the upper end, the age can be increased by say 1–4 years. This ensures that at the original upper age the curves are estimated with much greater precision, while at the new upper age, the relatively low precision does not matter.

Another age-related issue is whether measurements should be taken at precise prespecified ages (e.g., at 3 months or 12 months), or whether they should be distributed uniformly within a given age range. In the past, the statistical techniques available to fit centiles to growth data required measurements to be grouped at specific ages, but this is no longer an issue. Even so, longitudinal studies are usually designed around a set of fixed ages when measurements are made, whereas cross-sectional surveys are likely to recruit subjects within specified age ranges. The advantages of fixed ages in longitudinal studies are partly administrative—that is, all the subjects are measured at the same ages—and also that velocities can be calculated over constant periods of time, such as monthly or yearly.

Sampling

The subjects in the reference sample should be selected from the target population in a way that ensures generalizability, ideally by random sampling. The sample may be a simple random sample or a complex multistage design involving clusters or strata. For example, a national sample might be based on randomly selected clusters of geographical areas, then random households within areas, then random children within households. The advantages and disadvantages of the different designs involve a trade-off between complexity (i.e., cost) and efficiency (i.e., precision of the estimates). See Armitage and Berry[13] for a fuller description of sampling designs.

Children of school age can be ascertained through their schools, which is more efficient than working through households. Conversely, children of pre-school age or those who have left school are difficult to sample randomly, and this can pose problems for obtaining representative samples over age ranges extending beyond school.

COLLECTING THE DATA

Having identified the reference population and sample, the next stage is to measure the subjects. This requires decisions about which measurements to make, how to make them, and how to ensure their quality.

Select Measurements

The choice of measurements depends on the aim of the study. Weight and height (or length in infancy) are obvious choices, as they are the two “whole body” measurements, they require relatively simple equipment to measure them, and taken together, they provide a measure of weight for height, such as body mass index (weight/height^2).

Skinfold thicknesses are a useful proxy for regional body fat, and the contrast of, say, triceps and subscapular skinfold gives a measure of fat distribution in limbs relative to the trunk. The main disadvantage of skinfolds is the considerable interobserver variation, which reduces their generalizability. And, they can be particularly difficult to measure in obese subjects.

Body circumferences, such as arm or waist, are simpler to measure than skinfolds and provide information over and above the other measurements described so far. Arm circumference (also known as *mid–upper arm circumference*, MUAC) is a useful alternative to weight for height for assessing wasting in malnutrition.[14] In addition, arm circumference and triceps skinfold together provide an estimate of arm muscle area.[15] Waist circumference is increasingly important as a risk factor for obesity and its sequelae in adults[16] and is likely to be studied more in children in the future.

Head circumference acts as a proxy for brain size and is usually of interest primarily in infancy when head growth is maximal.

Body proportions can be studied by measuring sitting height or cristal height and expressing it as a fraction of height. Leg length is increasingly seen as a proxy for growth in early life and is important in life course studies.[17] Body widths, such as bi-iliac width or biacromial width, are for more specialized anthropometry studies.

Choose Location and Personnel

The next questions are these: Who will take the measurements, and where will these observers be based? Depending on the size of the survey, the observers may be existing anthropometrists, school nurses, practice nurses, or research nurses; alternatively, they may be recruited specifically for the survey. One measuring team may be based centrally, and travel to each region in turn, or teams may be based in each region that make use of local staff. The measurements can be made in subjects' houses or invited to a central meeting place, like a clinic or school. The choices depend on the ages of the subjects, their geographic spread, and the cost and availability of staff members. The choice between central and local measuring teams depends on the number of measurement regions, the number of subjects, the time available for the survey, and the likely compliance of subjects and their parents.

Equipment and Technique

Anthropometry is the primary focus of growth studies, so it is essential for the measurements to be of the highest possible quality. This requires attention to the instruments used; their calibration and maintenance; the training of observers in terms of technique, precision, and accuracy; and in particular to quality control throughout the study. For long-term studies, this involves regular training sessions where observers meet together to assess intra- and interobserver variation by measuring and remeasuring small groups of children.

For details of measurement technique and quality control, Weiner and Lourie[18] and Cameron[19] give comprehensive accounts.

CLEANING THE DATA

There is a grave temptation, once the data have been collected, to immediately start analyzing them—this is a mistake. An important preliminary stage is to *look* at the data, to search out errors of measurement or coding and fix them. Left untended these errors can seriously affect the validity of the analysis.

Diagnostic Plots: Marginal and Conditional

The key to data cleaning is the inspection of diagnostic plots, which fall into two categories: marginal and conditional. A marginal plot is a plot of one variable on its own, typically a histogram, showing the distribution of the measurement. This plot highlights the presence of any outliers and indicates the broad distributional shape of the variable; that is, whether it is normally distributed (bell shaped) or if there is some skewness (one tail, usually the right, longer than the other), kurtosis (heavy tails), or bimodality (with two peaks). With suitable software, it is possible to draw the histogram, highlight each outlier, check the corresponding data, and correct or eject as appropriate, all very quickly. An example of such a package is Data Desk (Data Description Inc), which is designed on exploratory data analysis (EDA) principles and has a strongly visual philosophy. As such, it is more suitable for data cleaning than command-line-based packages like SPSS or SAS.

Marginal diagnostic plots are useful for identifying the most obvious outliers, but they fail to pick up many others. For example, consider a height of 160 cm incorrectly coded as 60 cm. In a data set covering 0–20 years this corresponds to an adult height appearing as an infant length, so a marginal plot will fail to spot it. However, a scatter plot of height versus age will cause it to stand out as an obvious outlier. This is a *conditional* diagnostic plot of height on age.

The conditional plot works well when two variables are reasonably highly correlated (height and age here). It can be very sensitive, and for measurements like height that have a small coefficient of variation (see later) and the correlation is high, it will spot outliers that are far less extreme than the preceding example.

Weight versus age works nearly as well, except that weight usually has a skewed distribution, with the right tail longer than the left. Spotting outliers here is more difficult, as the individual points in the extreme right tail (i.e., at the top of the scatter plot) are spread further apart, and so appear to be more extreme, than those to the left. It is tempting to treat all those in the right tail as outliers, but this is generally not wise.

Ideally, the scatter plot needs to be redrawn so that the variable is approximately normally distributed, which ensures that the two tails are spread out roughly equally. This can be done using a power transformation (see later). The search for outliers is then more balanced in the two tails.

To help in the identification of outliers, it is useful to have an objective criterion, particularly for outliers that are not "barn door" obvious. Working with SD scores rather than the original measurements is useful as the age and sex differences are adjusted out, and weight or height for the entire data set can be plotted as a marginal diagnostic plot without involving age.

What is a reasonable range of values for the SD scores? A useful cutoff is ±5—the chance of a genuine point outside this range is vanishingly small (3 in 10 million), so even for large sample sizes of 10,000–20,000, such points are highly likely to be wrong. For appreciably smaller sample sizes, a tighter cutoff of, say, ±4 can be used, corresponding to a chance of 3 in 100,000.

The way to deal with outliers is to go back to the original coding form and look for something obviously wrong. In longitudinal studies it should also be possible to check the consistency of the subject's measurements on other occasions. Often an error will be found that can be corrected. But there will be occasions when the measurement is apparently correct, and the question then is whether or not to retain it in the data set.

There ought to be very few such points, so that they can be described and justified on an individual basis when the analysis is written up. Statistically, there is a case for omitting them even though they are correct, as they may challenge the assumptions made by the analysis. An analysis that is not robust to outliers may be seriously affected; an example is regression analysis where a single outlying point can alter a multiple regression equation dramatically.

ESTIMATING DISTANCE CENTILES

Once the data are clean, work can start on fitting the centiles. The process of fitting distance centiles to data involves a series of choices. Is age to be treated as continuous or grouped, such as by whole years? Can the measurement be assumed to be normally distributed at all ages, or is some form of adjustment needed? And, how should the centile curves be modeled—what form of equation is to be used? These issues are discussed in turn.

Age Grouped or Continuous

Splitting the data into distinct age groups is the traditional approach to centile fitting. Within each group, age is less critical and the distribution can be characterized across all the data; for example, as the mean and SD. These summary statistics can be adjusted for minor age effects,[20] plotted against age to represent the whole age range, and summarized by smooth curves drawn through them, one curve for the mean and one for the SD. Together the two curves allow any centiles to be drawn assuming that the distribution is normal, using the formula

$$\text{Centile}_{100\alpha} = \text{mean} + \text{SD} \times z_{\alpha} \qquad (18\text{-}1)$$

where z_{α} is the normal equivalent deviate for the required distance centile, and mean and SD are values read off the curves at a particular age. For the median or 50th centile (Centile_{50}) $z_{0.5} = 0$, while for the 3rd centile (Centile_3) $z_{0.03} = -1.88$. Values of Centile for a series of ages can be plotted against age to give the required centile curve.

But, splitting the data into age groups is inefficient and arbitrary, and age is better treated as a continuous variable. This then becomes a form of regression analysis, where a curve representing the mean is fitted to the data plotted against age. A separate curve needs to be fitted representing the SD, and several iterative methods have been proposed for this.[21–24] Again the outcome is two curves, Mean and SD, which can be plugged into Equation 18-1 to provide any required centile curves.

Distributional Assumptions

The previous section assumes that the data are normally distributed, so that the mean and SD are summary statistics for the distribution at each age. Usually, this applies to measurements with relatively low variability, such as height or head circumference, where the coefficient of variation is less than 5%. But other, more variable measurements, such as weight or skinfold thickness, have distributions with some degree of right skewness. Here the assumption of normality does not hold and a different approach is needed.

In the past, the centiles for such measurements were obtained empirically; that is, grouping the data by age, sorting the data into order, and reading off the required centiles. The resulting centile values for each age group could then be plotted against age and smooth curves fitted through them. This led to a set of centile curves that avoided assuming an underlying distribution, normal or otherwise. The American NCHS reference[25] was constructed in this way. But it is an inefficient process, as it requires age to be grouped. When age is treated as continuous, the methodology goes under the general name quantile regression,[26] and in more recent years it has been extended.[27,28] One disadvantage of quantile regression is that the centile curves may touch or even, in extreme cases, cross.

Another way to handle skewness is to transform the data in some way to bring the distribution closer to normal, two common transformations being the Box-Cox power transform[29] and the shifted log transform.[30] Effectively, this introduces a third parameter, in addition to the mean and SD, to compensate for skewness in the distribution at each age. The value of the parameter may be constant (e.g., transforming all the data to logarithms), or it may change with age in the same way that the mean and SD change.

The concept of an age-varying adjustment for skewness was first proposed by Van't Hof, Wit, and Roede[31] and extended and formalized by Cole.[32] Based on the Box-Cox transformation, Cole called it the *LMS method*, the three letters *L-M-S* representing, respectively, λ, the Box-Cox power; μ, the median; and σ, the coefficient of variation. The median is estimated from the mean on the transformed scale, where the distribution is symmetric, as the skewness has been removed. The coefficient of variation (CV) is preferred to the SD, because the SD, like the mean, tends to increase with age, whereas the CV is more constant through childhood, and indeed is often similar in infancy and adulthood. The quantities λ, μ, and σ have corresponding smooth curves plotted against age, estimated by maximum likelihood, and these L, M, and S curves together define any required centile curve using the equation

$$\text{Centile}_{100\alpha} = M(1 + LSz_\alpha)^{1/L} \tag{18-2}$$

where, as before, z_α is the normal equivalent deviate corresponding to the required centile. Substituting $L = 1$ for a normal distribution gives the simpler formula

$$\text{Centile}_{100\alpha} = M(1 + Sz_\alpha) = M + MSz_\alpha$$

which, bearing in mind that M is the mean, S the coefficient of variation, and MS the standard deviation, is the same as Equation 18-1.

An immediate spin-off of this approach is that skew data, in addition to those that are normally distributed, can be expressed as SD scores simply by rearranging Equation 18-2:

$$z = \frac{\left(\dfrac{\text{measurement}}{M}\right)^L - 1}{LS} \tag{18-3}$$

Setting $L = 1$ in Equation 18-3 gives the formula

$$z = \frac{\left(\dfrac{\text{measurement}}{M}\right) - 1}{S} = \frac{\text{measurement} - M}{MS}$$

which is the usual formula for calculating the SD score. This ability to express measurements as SD scores, irrespective of whether or not they come from a skewed distribution, leads to substantial simplifications in the analysis of anthropometry data (see later).

Cole[32] originally described the LMS method for distinct age groups but later extended it to continuous age.[33] Variations on the same general principle, with the skewness adjusted for in different ways, have been proposed by several authors.[28,34–38]

Healy, Rasbash, and Yang[39] suggested a quite different way of dealing with nonnormality that links the two methods just described. Their empirical centiles are first smoothed by scatter-plot smoothing,[40] then they are fitted by low-order polynomials in time t, where the coefficients of the polynomials are constrained to themselves follow low-order polynomials in z, the normal equivalent deviates corresponding to the centiles. In this way, the centiles are estimated as separate curves, but their shapes and the spacing between them are constrained to provide a consistent and regularly spaced set of centiles. Healy subsequently found that his method was less effective than a Box-Cox or shifted log transform for handling non-normally distributed data.[41]

Form of Smoothing

The simplest form of curve to use for smoothing data is a low-order polynomial, such as a linear, quadratic, or cubic curve. The polynomial is easy to fit using regression analysis, and the regression coefficients provide a parsimonious summary of the fitted curve. But the substantial disadvantage of polynomials, particularly higher-order polynomials applied to data with complex age trends, is that they behave poorly at the extremes of the data. Edge effects mean that the polynomial is often a poor fit at the youngest and oldest ages, and the curve may be unacceptably "wiggly" in between.

Fractional polynomials[42] largely avoid these problems. The conventional polynomial, containing terms with successive integer powers of age (t, t^2, t^3, etc.) is replaced by an equation with selected powers of age, the set of permissible powers being integer powers in the range –2 to +3 and certain nonintegral or zero powers; for example, $\sqrt{t}$, $\log(t)$ or $1/t$. As an example, the growth curve described by Earl Count nearly 60 years ago[43] is a fractional polynomial:

$$Y(t) = \beta_0 + \beta_1 t + \beta_2 \log(t)$$

Fractional polynomials are extremely effective at modeling the shapes of curves where both the curve and its slope either increase or decrease monotonically, as happens with anthropometry during gestation and in the preschool period. But they are less useful over longer periods of time, where either the measurement or its velocity changes nonmonotonically with age. Height in childhood and adolescence and body mass index during childhood are two examples where fractional polynomials are insufficiently flexible to model the underlying trends—height because of the pubertal growth spurt and body mass index because of the rise, then fall, then second rise.[44]

Tailor-made parametric growth curves have been developed for certain measurements, such as the Jenss-Bayley curve for weight or length in infancy,[45] the Preece-Baines curve for height in puberty,[46] and the JPA-2 curve for height from birth to adult.[47] In general, they are parsimonious (with between four and eight parameters to be estimated) and provide a good fit to the data. As such, they are useful functions to estimate the mean or median curves described in the previous section.

But these special parametric growth curves are not available for all measurements, and in any case, they are not well suited to modeling age-related trends in, say, the SD or the skewness, except in very simple cases. For this, a more flexible approach is needed.

Spline smoothing and kernel smoothing are two related techniques that have proven effective for fitting smooth curves to data. Both are forms of local moving averages of the data, where the range of data averaged at each age (bandwidth) and the weightings applied to the data (weighting function) are varied in different ways.[48,49]

Kernel regression has generally been applied to quantile regression,[28,50–52] while natural smoothing splines have been preferred for semiparametric regression applications like the LMS method.[33]

Available Software

To simultaneously estimate curves for the mean and SD, Aitkin[21] provides general linear modeling macros while Altman's method[22] can be fitted by any package that handles linear regression. Similarly, polynomials are straightforward to fit in any package, while fractional polynomials either can be fitted manually or Stata has a do-file to fit them automatically.

Healy's method can be fitted using his package, GROSTAT II; and Royston provides Stata do-files to fit the shifted log, Box-Cox, and exponential transforms with fractional polynomials. Cole has a program to fit the semiparametric LMS method using cubic smoothing splines.

VARIANTS OF THE DISTANCE CHART

The discussion so far has focused on the simplest form of distance chart. But other forms of chart based on the distance chart also deserve a mention.

Puberty

Puberty is a time when children of the same age can differ dramatically in size, due to differences in their stage of maturation.[53] In principle, this could be represented on a chart with an extra scale for stage of maturation, but it would need to be plotted in three dimensions. As a compromise, a modified version of the distance chart has been developed that partially addresses this issue.

Variability in the timing of puberty causes the median curve on the chart to be flattened relative to the growth curve of individual children.[54] The slope of the median curve at its steepest, which represents the measurement's peak velocity, is biased downward; that is, it is less than the peak velocity in individual children. There are broadly two ways to respond to the bias—ignore it or adjust for it.

Tanner and Whitehouse minimized it by modifying the shapes of the height centile curves during puberty.[55] They drew them as steeper than they actually were, so that instead of representing the median height at each age, they followed the growth curve of a hypothetical child of average height, average height velocity, and average growth tempo (tempo indicates the rate of maturation). Called a *tempo-conditional chart*, its advantage was said to be that it minimized centile crossing as the median curve is similar in shape to a growth curve.

In practice, it does not eliminate centile crossing. Any child whose height distance, velocity, or tempo is not average will cross centiles at some point during puberty. The one advantage of the tempo-conditional chart over the conventional chart is that its median curve looks more like a growth curve. Its disadvantage is that the "median" curve no longer represents the population median height in puberty, and similarly the other "centile" curves do not correspond to the population centiles.

The alternative approach to the bias is to ignore it, which is what a conventional distance chart does. The British 1990 reference is an example. Here the centile curves provide unbiased estimates of the distribution centiles at all ages including puberty.

Neither approach satisfactorily solves the problem of assessing both distance and velocity at puberty. Opinion is divided as to which is better.

Repeated Measures

The distance chart is usually based on data where each subject provides one measurement. But quite often this does not hold—subjects in longitudinal or mixed longitudinal designs have more than one measurement, and the question is, What to do with them? There are three schools of thought on this: (1) restrict the data to one measurement per subject (the first or a random choice), (2) use the mean value for each subject, or (3) use all the data for each subject, treating them as unrelated.

The first alternative is safe but conservative—it ensures that no measures are repeated, but it also wastes data. The second approach is not correct, as it introduces differential weighting. The variability of the mean of several points is smaller than for a single point, so the measurement error for subjects with averaged repeated measures is artificially reduced.

The third alternative, to retain all the data, is probably the best, although this is controversial. The issue comes back to distance versus velocity, in that a distance chart contains no information about velocity. The distance centile curves can be thought of as a series of snapshots of the measurement distribution at different ages, smoothly joined across ages. Each such snapshot is unrelated to the others, so it does not matter if a subject is represented in more than one snapshot, the shapes of the centiles are not affected.

What *is* affected is the precision with which the centile curves are calculated. Consider an extreme example, two surveys with 1000 points each, one a longitudinal study of 50 subjects measured annually from 0–19 years old, the other a cross-sectional survey of 1000 children 0–19 years old. If the two sets of subjects are drawn randomly from the same reference population, then on average the two sets of fitted centiles will be the same—both will be unbiased estimates of the population centiles. The longitudinal centiles will be far less *precise*, in that the between-subject variability will be based on 50 subjects rather than 1000, and the confidence intervals for each centile will be wider, but the centiles themselves will (on average) be the same. Wade and Ades[56] argued the case more formally, showing that adjusting explicitly for the correlation between repeated measures does not materially alter the shapes of the fitted centiles.

This may appear counterintuitive, but Healy[57] showed it to be *exactly* true for the analagous situation of paired organs in large samples. Here, subjects provide two measurements (e.g., two arms or two ears), and Healy showed that the correct approach is to ignore the pairings and treat the data as independent.

In general, if the repeated measures data are balanced—that is, every subject has measurements at the same age (as would be the case in a longitudinal study with no missing data)—then the repeated measures structure can be ignored for the purposes of constructing a distance chart. If some of the data are missing, then so long as they are missing at random, the repeated measures structure can be ignored.

INTERPRETING THE CURVES

The previous section shows how growth references can be summarized in terms of three curves summarizing the mean or median, variability, and skewness of the measurement through childhood. These curves provide useful information about the growth processes underlying the measurement.

Take the LMS method, for example, where the three curves are the median (*M*), the CV (*S*), and the Box-Cox power to minimize skewness (*L*). Figures 18-1 and 18-2 show *M* and *S* curves by sex for the British 1990 height and weight references.[8] The median curves are familiar in shape, but the CVs have an unexpected dip soon after birth. In proportional terms, the SDs of height and weight fall until about 9 months after birth, then rise until puberty, 2 years earlier for girls than boys, and then fall again to values near those seen at birth. There is considerable centile crossing in both weight and length during the first year, and this process obviously reduces variability in the first few months. Then a different process starts to increase the variability, which continues until puberty and drops away again. This process must represent heterogeneity in the rate of maturation.

The distribution of height is close to normal but for weight it is appreciably skew and adjusted for using the Box-Cox power transformation. Figure 18-3 shows the *L* curves by sex for the weight reference, the Box-Cox power as it changes with age, and for comparison, the first derivatives of the weight *M* curves. The *L* curve in Figure 18-3A has a different shape from the *M* or *S* curves in Figure 18-2, falling from birth until puberty, when it rises briefly then falls again. Its general shape is reminiscent of the weight velocity curve seen in Figure 18-3B. Calculated from weight differences over 1 year, it is obviously not a true velocity curve, but it gives an idea of the change in weight velocity during childhood. The similarity of the two graphs in Figure 18-3 shows that skewness is linked inversely to acceleration. When weight decelerates rapidly in the first year (i.e., weight velocity falls), the *L* curve also falls and skewness increases, while during puberty, when

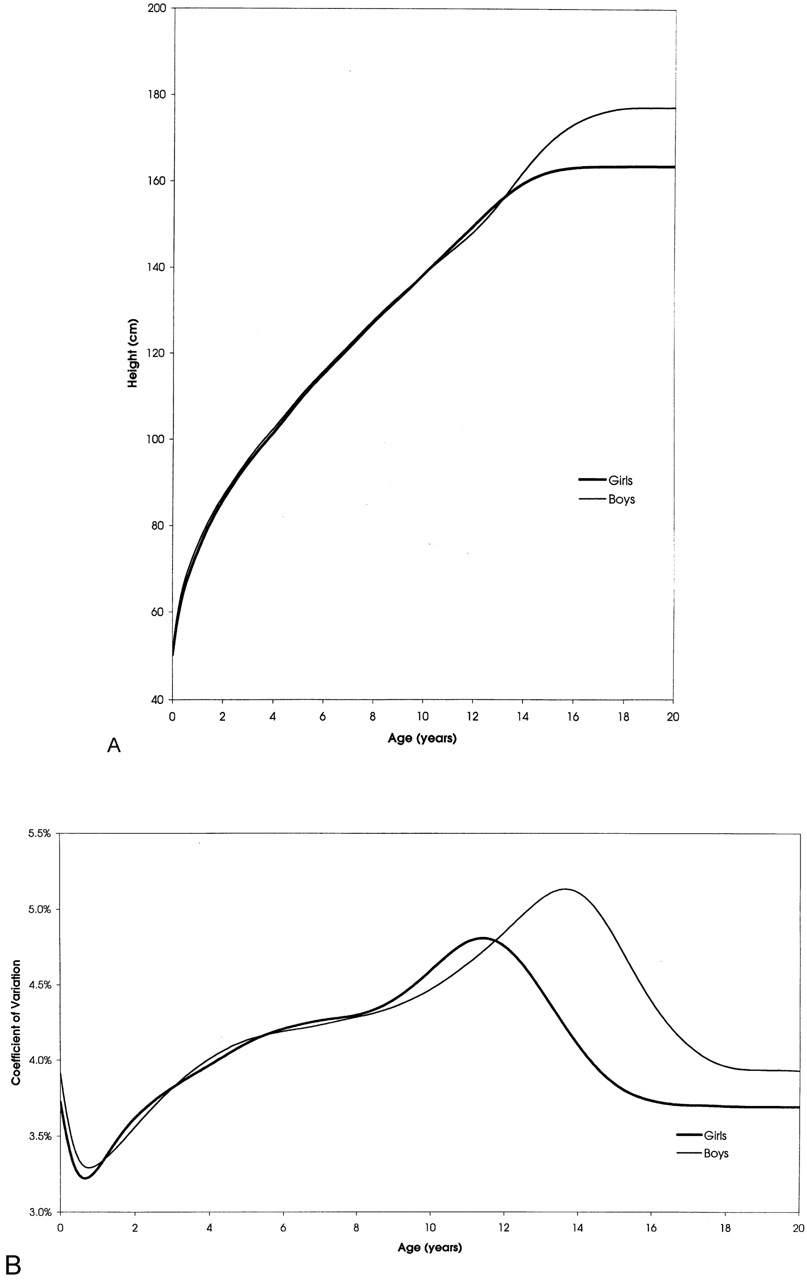


FIGURE 18-1 *M* and *S* curves for height by sex in the British 1990 growth reference.[3] The *M* curves (A) are median height by age, and the *S* curves (B) the coefficient of variation.

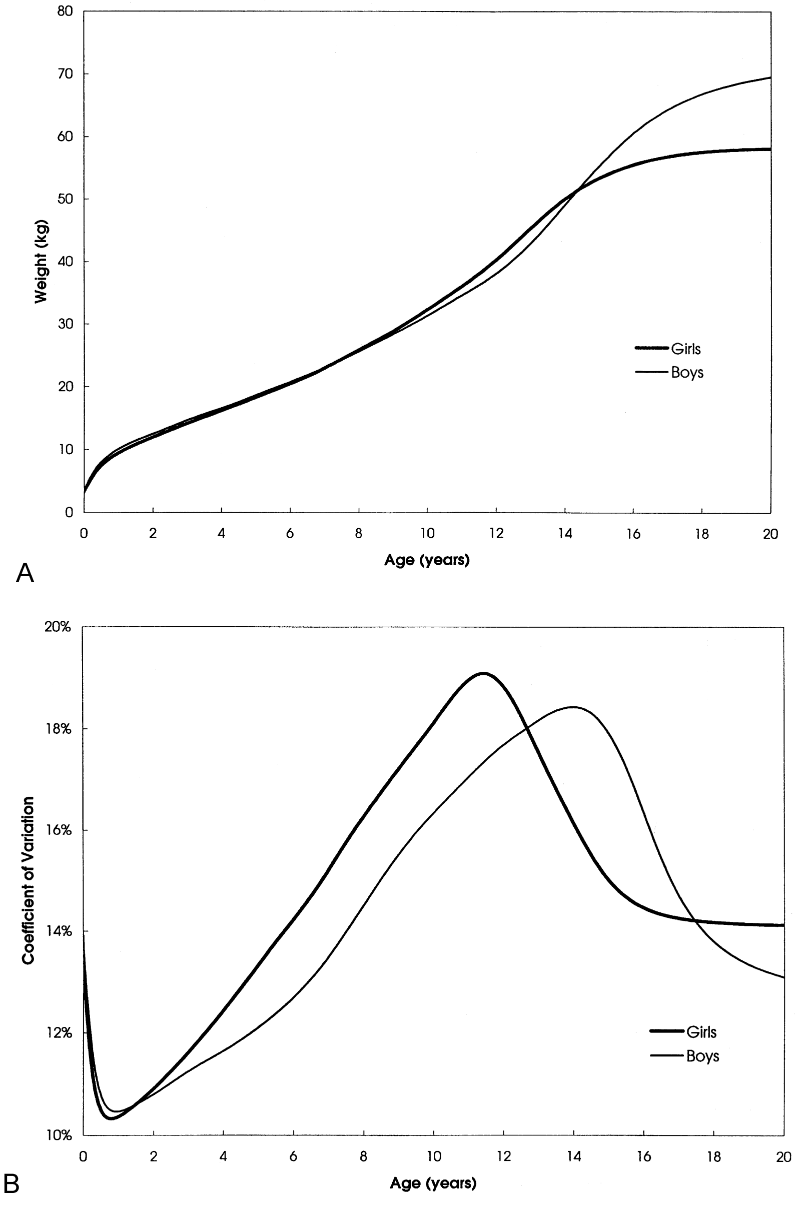


FIGURE 18-2 *M* and *S* curves for weight by sex in the British 1990 growth reference.[3] The *M* curves (A) are median weight by age, and the *S* curves (B) the coefficient of variation.

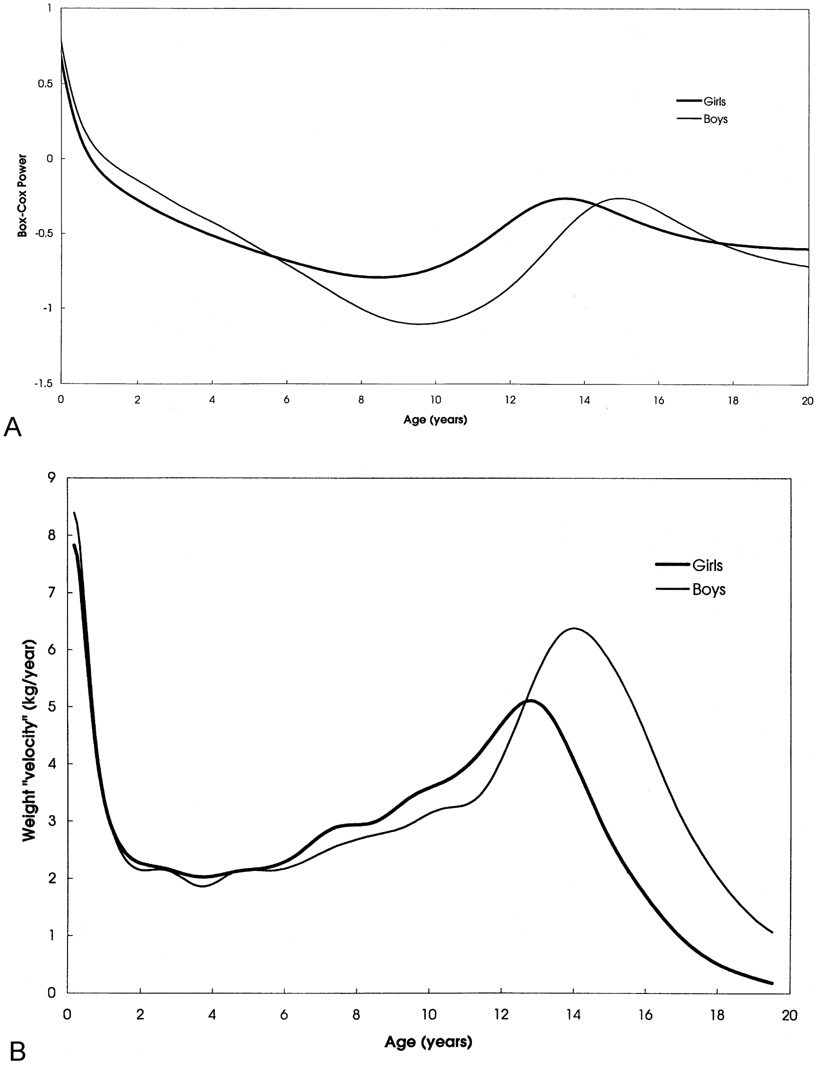
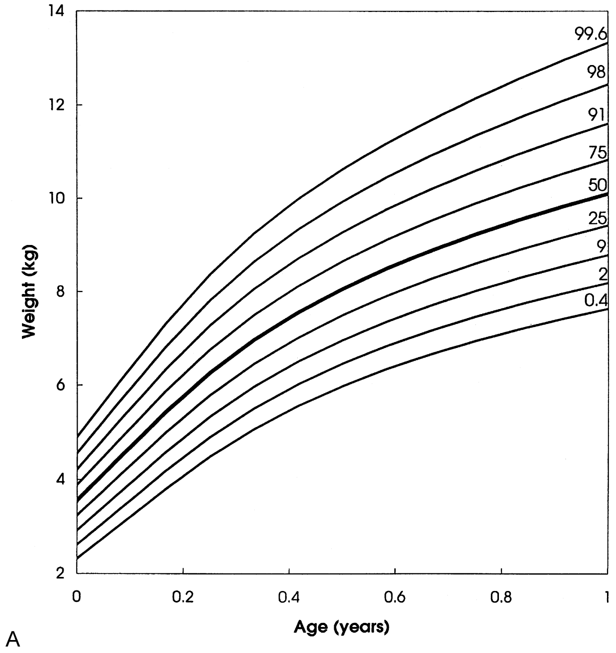


FIGURE 18-3 *L* curves for weight by sex in the British 1990 growth reference,[3] and for comparison, slopes of the weight *M* curves. The *L* curves (A) are the Box-Cox power transformation needed to remove skewness at each age, and the slopes of the *M* curves, (B) a form of weight "velocity."

weight velocity increases then decreases, the *L* curve rises then falls and skewness does the reverse.

These insights into the processes underlying height and weight growth are in addition to the practical value of the charts they define.



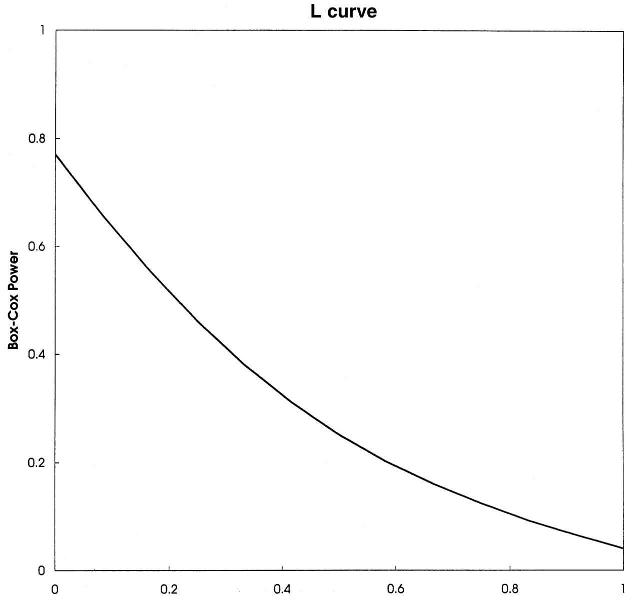


FIGURE 18-4 (A) Centiles for weight in British male infants from 0–1 year, with the corresponding *L* (B) and *S* (C) curves. The *L* curve is near 1 at birth, so the centiles are normally distributed and equally spaced, while by 1 year, the *L* curve has fallen to 0, indicating right skewness requiring a log transformation, and the centiles are more widely spaced above the median than below.

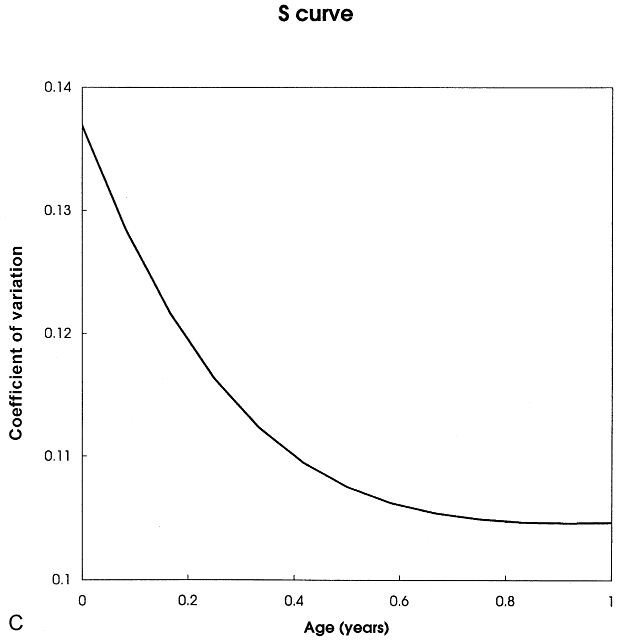


FIGURE 18-4 *(continued)*

Figure 18-4 shows the nine centiles corresponding to the British 1990 weight reference for boys in the first year, along with the corresponding L and S curves. The L curve falls from near 1 at birth to near 0 at 1 year, and this causes the skewness of the centiles to increase.

CHARTING VELOCITY

Unconditional Velocity

The distance chart treats repeated measures data as unrelated, so how is velocity to be assessed?

Traditionally, velocity has been measured in the original units of measurement, such as cm/yr for height velocity, which leads to a velocity chart with an interesting shape where the centile curves highlight the pubertal growth spurt.[58] The simplest way to construct a velocity chart is in the same way as a distance chart, except that paired data from individual subjects are needed to calculate each subject's velocity. In addition, the timing of the pairs of measurements needs to be exact, such as 1 year apart for height, as this affects the variability of the velocity.[59]

The effect of puberty on the distance chart applies equally to the velocity chart, and Tanner and Whitehouse[55] produced tempo-conditional velocity charts to match their distance charts.

The disadvantage of this whole approach to velocity is that it requires a separate chart from the distance chart and the data need to be plotted twice, once for distance and once for velocity. Further, the individual velocities need to be calculated before they are plotted.

An alternative is to focus on centile crossing. Velocity, compared to average velocity for age, is effectively centile crossing, so it is logical to measure velocity in centile units. Statistically, SD scores are more appropriate than centiles (as the scale is not bounded at 0 and 100), so the velocity can be expressed as the rate of change in the SD score. A child whose centile (and hence SD score) remains constant over time (i.e., no centile crossing) has zero rate of change, and this corresponds to the median velocity.

Measuring velocity on the SD score scale has two benefits: The change in SD score can be assessed directly, and the corresponding velocity can be represented visually on the distance chart.[60] To express centile crossing as a velocity centile, the variability of centile crossing needs to be known. This comes directly from the standard deviation of the change in SD score, which surprisingly depends only on the correlation r between SD scores at the two ages the child is measured.[61] The actual formula is

$$\text{SD of SD score change} = \sqrt{2(1-r)} \tag{18-4}$$

Take for example weight from birth to 1 year. The correlation between weight SD scores at birth and 1 year is 0.59,[62] so the SD of the SD score change from birth to 1 year is

$$\sqrt{2(1-0.59)} = \sqrt{2\times 0.41} = \sqrt{0.82} = 0.91$$

The mean change in SD score over the year is 0, and 95% of infants are within ±2 SDs of this; that is, changes in the range -1.82 to $+1.82$ SD score units.

The same information can be used to express an individual infant's SD score change as a velocity centile. Take a child whose weight is on the 16th centile at birth (SD score = -1) but who has caught up to the median by 1 year—this centile crossing upward is an increase of 1 SD score. A change in SD score of $+1$ corresponds to $1/0.91 = 1.1$ SDs, corresponding to the 86th centile for SD score change, or equivalently the 86th velocity centile (assuming velocity is normally distributed). So about 86% of infants followed from birth to 1 year can be expected to cross centiles upward by 1 SD score or less.

Conditional Velocity

This is a simple and fairly intuitive way of assessing centile change. However, there is a complication due to the statistical phenomenon of regression to the mean. This states that, on average, the centiles of individuals (or groups of individuals) followed over time will tend to become less extreme, more ordinary, closer to the median. As a result there is a built-in negative correlation between the starting centile and the change in centile over time—a child on a low starting centile, on average, crosses centiles upward (i.e., exhibits catch-up growth), whereas the opposite occurs for a child starting on a high centile. Cole[62] discussed this in the context of infant weight gain.

This form of velocity is known as *conditional* velocity; that is, conditional on the previous measurement. Velocity as defined in the previous section is, by analogy, called *unconditional* velocity.

To adjust for regression to the mean, the SD score on the second occasion is compared with what would be predicted from the first occasion. The prediction comes from linear regression analysis:

$$z_2 = r \times z_1 \tag{18-5}$$

So instead of the change in SD score over time, for example, $z_2 - z_1$, an adjusted change is used, $z_2 - r \times z_1$, where again r is the correlation between the two SD scores z_1 and z_2. The SD of this adjusted SD score change is $\sqrt{1 - r^2}$, which is smaller than Equation 18-4.

In the preceding example, where the SD score increases from –1 to 0 from birth to 1 year, the adjusted increase in SD score is

$$z_2 - r \times z_1 = 0 - 0.59 \times -1 = 0.59$$

which is rather less than the unadjusted increase of 1. The corresponding SD is $\sqrt{1 - 0.59^2} = 0.81$, so the velocity SD score is 0.59/0.81 = 0.73, corresponding to the 76th velocity centile. So, an infant with a low birth weight would be expected to catch up to some extent, and adjusting for this puts his or her velocity at the 76th rather than the 86th centile.

This process can be reversed to define a given velocity centile in terms of the SD scores at the start and end of the interval. For a notional child with SD score z_1 measured at age t_1 and z_2 at age t_2, where the correlation between z_1 and z_2 is known to be r and the required velocity centile corresponds to SD score z_v, then the four quantities are related as follows:

$$z_2 = r \times z_1 + \sqrt{1 - r^2} \times z_v$$

This relationship allows a velocity centile to be represented as a line on the distance chart. It starts at the measurement corresponding to z_1 at age t_1 and ends at the measurement corresponding to z_2 at age t_2, and the *slope* of the line is the velocity. Several such lines can be drawn between t_1 and t_2 by choosing different values for z_1, so whatever the size of the child there will be a velocity centile line near his or her data plotted on the chart.

Contiguous lines can be drawn for later intervals, such as from age t_2 to t_3 and later ages, by choosing the calculated value of the second SD score (z_2 in the equation) for each interval as the starting SD score (z_1 in the equation) for the next interval. This gives a set of curves, which cut across the distance centiles, and the slopes of the curves (*not* their positions) indicate the velocity centiles at each age. Velocity centiles below the 50th cross distance centiles downward, while those above the 50th cross upward. In general, the curves are not parallel at each age, showing that expected velocity depends on the size of the child. Figure 18-5 shows the distance chart for weight in infancy, with the second velocity centile curves superimposed, for measurements taken 4 weeks apart.

A child's growth is assessed on the chart by comparing the slope of his or her line joining successive pairs of points with the slope of the nearest velocity centile curve over the same age range. If the two lines are parallel, then the child's velocity is equal to the nominal velocity centile. If the child's line is steeper, he or she is above the centile; if shallower below it.

The addition of these velocity curves to the distance chart can make the chart hard to read. In principle, more than one set of curves could be provided, such as both the 2nd and 98th velocity centiles, but the chart rapidly becomes too cluttered to be useful. An alternative is to provide each set of velocity centile curves as a transparent plastic overlay that can be placed on the distance chart; this keeps the chart simple while providing an assessment of velocity. It also requires the data to be plotted only once and avoids calculating velocities.

CONDITIONAL REFERENCES

Conditional velocity is just one example of the family of conditional references. Equation 18-5 shows how one SD score is predicted from another, where the two SD scores correspond to consecutive measurements in one child. But the meanings of the two SD scores are quite general—they could, for example, be birth weights for two siblings, giving a reference of birth weight conditional on sibling birth weight, or heights of parent and child (i.e., a reference of height conditional on parental height).[63] By specifying the reference on the SD score scale the only extra information for the reference is the correlation between the pairs of measurements.

PRINTING THE CHART

The final stage in the production of a growth reference is to print and distribute the charts. As with any other marketable commodity, it pays to design the chart to suit its users, and extensive consultation is needed to ensure that the format of the chart is optimal. This involves issues to do with the choice of centiles on the chart (discussed earlier), the age ranges and combinations of different measurements to include in particular charts (for example, weight, length, and head circumference on a single chart in the first year), the choice of age scale (e.g., decimal or in months for the first year), and the chart's general appearance in terms of orientation (portrait or landscape), color scheme, scales, and gridlines. They make a big difference to the usability of the chart in clinical practice.

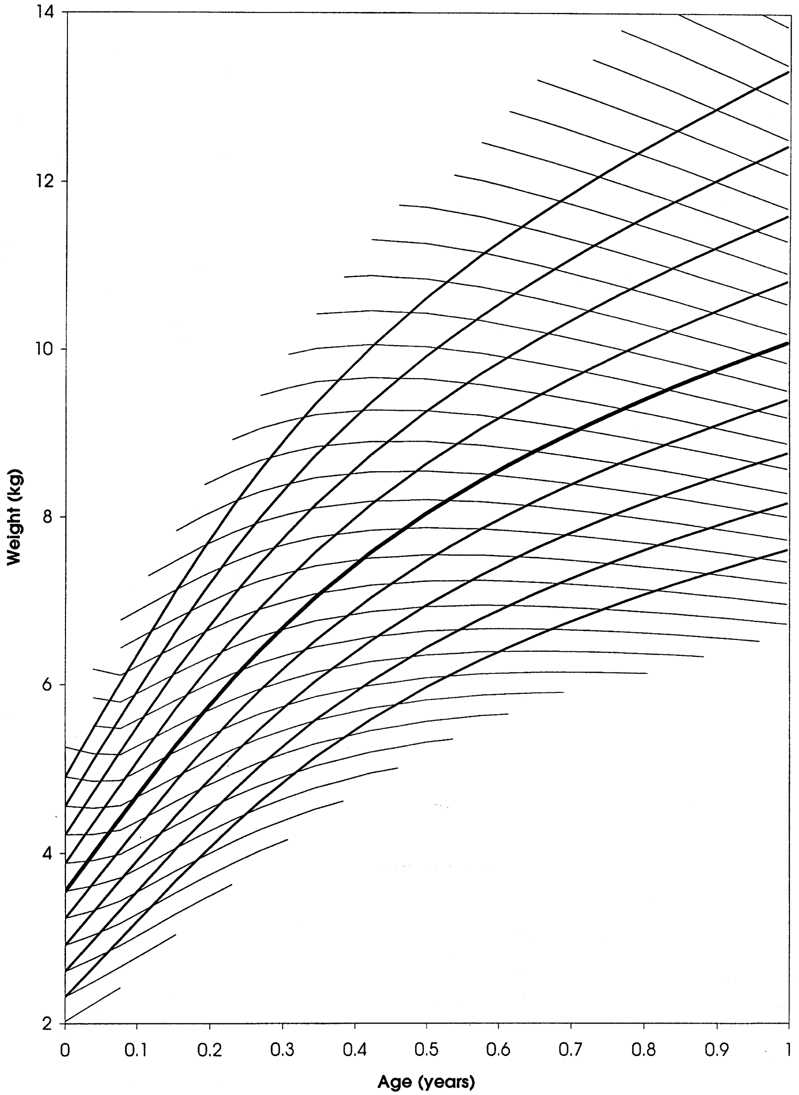


FIGURE 18-5 The boys weight distance centiles of Figure 18-4 with lines superimposed representing the second conditional velocity centile. The slope of the line joining an infant's successive weights measured 4 weeks apart is compared with the slope of the nearest velocity centile line. See the text for details.

Remember that different users, such as endocrinologists versus community pediatricians versus health visitors, use the charts in different ways, so it is important to canvass opinion as widely as possible before settling on the final design. And providing some forum for feedback can ensure that later printings of the charts incorporate modifications to improve them further.

WHEN TO REPLACE

Once charts have been available for a period of time, the question arises, Should they be updated? Due to secular trends in growth, children change in size and/or shape after the chart is produced. Updating the chart ensures that the centiles continue to reflect accurately the proportions of children outside the extreme centiles. An interval of about 15 years between updates is typical; for example, the Dutch national growth surveys took place in 1965, 1980, and 1997. But two disadvantages to updating charts also need to be borne in mind.

First, it takes a very long time for a new chart to displace the old. This is due partly to ignorance (the new chart is not widely known about), partly to inertia ("I prefer the chart I'm used to"), and partly to finance (purchasing officers expect existing stocks of charts to be exhausted first).

The second disadvantage is more subtle: The secular trend may be toward less optimal growth; for example, the recent increase in obesity that has shifted weight and body mass index centiles upward. If the centiles are used to define overweight, such as the 91st centile on the body mass index chart,[44] then this provides a nominal prevalence of 9% overweight. Such a figure was appropriate at the time the chart data were collected (1990), but with the trend to increasing fatness, the prevalence has since increased. If the chart were to be updated and the 91st centile shifted upward the prevalence of overweight would revert to 9%, but it would not be comparable with the 9% prevalence on the previous chart—the prevalence rates before and after would not be comparable.

For this reason the British body mass index chart has been "frozen" in time and will not be updated.[64] In effect, the chart has become a standard rather than a reference—it reflects body mass index at an earlier time when the population was less fat than it is now.

CONCLUSION

The process of producing new growth charts involves several important stages. The choice of reference population and sample, collecting and recording the anthropometry, analyzing the data and printing the chart, together require the skills of specialists in many different areas. The outcome should be a set of charts that are effective in recording and assessing the growth of the children they serve.

REFERENCES

1. Tanner JM. A History of the Study of Human Growth. Cambridge: Cambridge University Press, 1981.
2. Dibley MJ, Goldsby JB, Staehling NW, Trowbridge FL. Development of normalized curves for the international growth reference: historical and technical considerations. Amer J Clin Nutr. 1987;46:736–748.

3. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross-sectional stature and weight reference curves for the UK, 1990. Arch Dis Child. 1995;73:17–24.
4. Cole TJ. Do growth chart centiles need a face lift? Brit Med J. 1994;308:641–642.
5. Chinn S, Cole TJ, Preece MA, Rona RJ. Growth charts for ethnic populations in UK [letter]. Lancet. 1996;347:839–840.
6. Cronk C, Crocker AC, Pueschel SM, Shea AM, Zackai E, Pickens G, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. Pediatr. 1988;81:102–110.
7. Ranke M B, Plüger H, Rosendahl W. Turner's syndrome: Spontaneous growth in 150 cases and review of the literature. Euro J Pediatr. 1983;141:81–88.
8. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. Stat Med. 1998;17:407–429.
9. Graitcer PL, Gentry M. Measuring children: One standard for all. Lancet. 2:297–299.
10. Tanner JM. Some notes on the recording of growth data. Hum Biol. 1951;23:93–159.
11. Falkner F. Twenty-five years of internationally coordinated research: Longitudinal studies in growth and development. Courier. 1980;30:3–7.
12. Garza C, De Onis M. A new international growth reference for young children. Amer J Clin Nutrit. 1999;70:169S–172S.
13. Armitage P, Berry B. Statistical methods in medical research. Oxford: Blackwell Science, 1987.
14. Briend A, Zimicki S. Validation of arm circumference as an indicator of risk of death in 1 to 4 year old children. Nutrit Res. 1986;6:249–261.
15. Rolland-Cachera MF, Brambilla P, Manzoni P, Akrout M, Del Maschio A, Chiumello G. A new anthropometric index validated by magnetic resonance imaging (MRI) to assess body composition. Amer J Clin Nutrit. 1997;65:1709–1713.
16. Han TS, Van Leer EM, Seidell JC, Lean MEJ. Waist circumference action levels in the identification of cardiovascular risk factors: Prevalence study in a random sample. Brit Med J. 1995;311:1401–1405.
17. Gunnell DJ, Davey Smith G, Holly JMP, Frankel S. Leg length and risk of cancer in the Boyd Orr cohort. Brit Med J. 1998;317:1350–1351.
18. Weiner JS, Lourie SA. Practical human biology. London: Academic Press, 1981.
19. Cameron N. The measurement of human growth. London: Croom-Helm, 1984.
20. Healy MJR. The effect of age grouping on the distribution of a measurement affected by growth. Amer J Phys Anthropol. 1962;20:49–50.
21. Aitkin M. Modelling variance heterogeneity in normal regression using GLIM. Appl Stat. 1987;36:332–339.
22. Altman DG. Construction of age-related reference centiles using absolute residuals. Stat Med. 1993;12:917–924.
23. Rigby RA, Stasinopoulos DM. A semiparametric additive—model for variance heterogeneity. Stat Comput. 1996;6:57–65.
24. Tango T. Estimation of age-specific reference ranges via smoother AVAS. Stat Med. 1998; 17:1231–1243.
25. Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF. NCHS growth curves for children birth–18 years. Vital and Health Statistics Series 11, No. 165. Washington, DC: National Center for Health Statistics, 1977.
26. Koenker RW, Bassett GW. Regression quantiles. Economet. 1978;46:33–50.
27. Koenker R, Ng P, Portnoy S. Quantile smoothing splines. Biomet. 1994;81:673–680.
28. Heagerty PJ, Pepe MS. Semiparametric estimation of regression quantiles with application to standardizing weight for height and age in U.S. children. J Royal Stat Soc C—Appl Stat. 1999;48:533–551.
29. Box GEP, Cox DR. An analysis of transformations. J Royal Stat Soc B. 1964;26:211–252.
30. Royston P. Estimation, reference ranges and goodness of fit for the three-parameter lognormal distribution. Stat Med. 1992;11:897–912.

31. Van't Hof MA, Wit JM, Roede MJ. A method to construct age references for skewed skinfold data, using Box-Cox transformations to normality. Hum Biol. 1985;57:131–139.
32. Cole TJ. Fitting smoothed centile curves to reference data (with discussion). J Roy Stat Soc A. 1988;151:385–418.
33. Cole TJ, Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. Stat Med. 1992;11:1305–1319.
34. Thompson ML, Theron, GB. Maximum likelihood estimation of reference centiles. Stat Med. 1990;9:539–548.
35. Royston P. Constructing time-specific reference ranges. Stat Med. 1991;10:675–690.
36. Wade AM, Ades AE. Age-related reference ranges—Significance tests for models and confidence intervals for centiles. Stat Med. 1994;13:2359–2367.
37. Royston P, Wright EM. A method for estimating age-specific reference intervals ("normal ranges") based on fractional polynomials and exponential transformation. J Royal Stat Soc A—Stat in Soc. 1998;161:79–101.
38. Sorribas A, March J, Voit EO. Estimating age-related trends in cross-sectional studies using S-distributions. Stat Med. 2000;19:697–713.
39. Healy MJR, Rasbash J, Yang M. Distribution-free estimation of age-related centiles. Ann Hum Biol. 198815:17–22.
40. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Amer Stat Assn. 1979;79:829–836.
41. Healy MJR. Normalizing transformations for growth standards. Ann Hum Biol. 1992;19:521–526.
42. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: Parsimonious parametric modelling (with discussion). Appl Stat J Royal Stat Soc C. 1994;43:429–467.
43. Count E. Growth pattern of the human physique. Hum Biol. 1943;15:1–32.
44. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Arch Dis Child. 1995;73:25–29.
45. Jenss RM, Bayley N. A mathematical method for studying growth in children. Hum Biol. 1937;9:556–563.
46. Preece MA, Baines MJ. A new family of mathematical models describing the human growth curve. Ann Hum Biol. 1978;5:1–24.
47. Jolicoeur P, Pontier J, Abidi H. Asymptotic models for the longitudinal growth of human stature. Amer J Hum Biol. 1992;4:461–468.
48. Wand M, Jones MC. Introduction to Kernel Smoothing. London: Chapman and Hall, 1994.
49. Green PJ, Silverman BW. Nonparametric Regression and Generalized Linear Models. London: Chapman and Hall, 1994.
50. Guo S, Roche AF, Baumgartner RN, Chumlea WC, Ryan AS. Kernel regression for smoothing percentile curves: Reference data for calf and subscapular skinfold thicknesses in Mexican Americans. Amer J Clin Nutrit. 1990;51:908S–916S.
51. Rossiter JE. Calculating centile curves using kernel density estimation methods with application to infant kidney lengths. Stat Med. 1991;1693–1701.
52. Ducharme GR, Gannoun A, Guertin MC, Jequier JC. Reference values obtained by kernel-based estimation of quantile regressions. Biometrics. 1995;1:1105–1116.
53. Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Scientific Publications, 1962.
54. Merrell M. The relationship of individual growth to average growth. Hum Biol. 1931:7–70.
55. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and the stages of puberty. Arch Dis Child. 1976;1:170–179.
56. Wade AM, Ades AE. Incorporating correlations between measurements into the estimation of age-related reference ranges. Stat Med. 1998;17:1989–2002.
57. Healy MJR. Reference values and standards for paired organs. Ann Hum Biol. 1993;20:75–76.
58. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Parts I and II. Arch Dis Child. 1966; 41:454–471, 613–635.

59. Cole TJ. The use and construction of anthropometric growth reference standards. Nutrit Res Rev. 1993;6:19–50.
60. Cole TJ. Growth charts for both cross-sectional and longitudinal data. Stat Med. 1994;13:2477–2492.
61. Cole TJ. Growth monitoring with the British 1990 growth reference. Arch Dis Child. 1997; 76:1–3.
62. Cole TJ. Conditional reference charts to assess weight gain in British infants. Arch Dis Child. 1995;73:8–16.
63. Cole TJ. A simple chart to assess non-familial short stature. Arch Dis Child. 2000;82:173–176.
64. Cole TJ, Power C, Preece MA. Child obesity and body-mass index [letter]. Lancet. 1999;353:1188.

ANNOTATED REFERENCES

The following volumes are recommended to students studying human growth and development. Most will be available through university libraries, but if financial resources allow it, some of the smaller, single-author volumes should be considered for purchase. It is recommended that the postgraduate student considering a career in teaching and research in which human growth and development form a core subject should use this reference list, and those of each of the chapters in this book, to build a personal reference library. This is not an exhaustive list but represents those volumes that I found particularly useful both for personal reference and for recommending to students as source references to the science of auxology.

Bogin B. Patterns of Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1999. Barry Bogin takes a biocultural approach to human growth and development. His research tends to concentrate on the relationship between migration and growth in both physical and social contexts, but this book is far more than that. It covers most aspects of growth, with a biocultural flavor and has particularly useful, interesting sections on Bogin's theories of the evolution of the pattern of human growth. The second expanded edition is preferred over the first edition.

Brook CGD, Hindmarsh P (eds). Clinical Paediatric Endocrinology, 4th ed. Oxford: Blackwell Science, 2001. Charles Brook's landmark volume, now in its fourth edition, continues to form the core source reference for comprehensive information on the endocrinological basis of human growth and its disorders. It is an excellent reference text for both clinical and nonclinical students.

Eveleth PB, Tanner JM. Worldwide Variation in Human Growth, 2nd ed. Cambridge: Cambridge University Press, 1990. Phyllis Eveleth was secretary to the International Biological Programme in the 1960s and 1970s and collected and collated growth data from throughout the world during this time. She and Tanner created the first edition of this book, in 1976, which rapidly became a classic reference work. They encouraged researchers to send them growth data and the result is the updated, expanded second edition. It is excellent in putting human growth within a broad environmental context.

Falkner F, Tanner JM. Human Growth: A Comprehensive Treatise, 2nd ed. New York: Plenum, 1986. This was the first multivolume, multiauthor text attempting to embrace the full expanse of the science of "auxology." This second edition is divided into three volumes, covering developmental biology and prenatal growth; postnatal growth and neurobiology; and methodology, ecological, genetic, and nutritional effects on growth. A recognized authority authors each chapter, and when first published, it was the most authoritative text on the subject. Bought by many university libraries, it is essential as background reading to introduce the many topics within this field.

Gibson RS. Principles of Nutritional Status Assessment. New York: Oxford University Press, 1990. See N. G. Norgan's comments within Chapter 7 on "Nutrition and Growth." Gibson's copious volume is recognized as *the* essential reference work for different approaches to nutrimental assessment and is fundamentally important within human growth research. There are sections on the dietary, anthropometric, and biochemical approaches to nutritional status assessment and a short section on clinical assessment.

Lohman TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics, 1988. This is the most comprehensive and detailed account of the methods used in anthropometry. It contains descriptions of almost every anthropometric technique used within human growth and includes useful information on reliability.

Malina RM. Growth, Maturation and Physical Activity. Champaign, IL: Human Kinetics, 1991. Robert M. Malina is recognized as the world authority on the relationship between physical exercise and human growth and development (see Chapter 15). This volume is the most comprehensive discussion of this relationship currently available.

Smith DW. Growth and Its Disorders. Philadelphia: W. B. Saunders, 1977. The book is a classic and still of great relevance. It has excellent introductory chapters on assessment techniques and the use of growth charts.

Smith, DW. Recognizable Patterns of Human Malformation: Genetic, Embryological and Clinical Aspects, 3rd ed. Philadelphia: W. B. Saunders, 1982. David Smith was the world expert on human malformation and collected his vast clinical and scientific knowledge into this volume. It went through two editions prior to his untimely death and a third expanded edition was published posthumously. It is an essential reference work for clinical students.

Tanner JM. Growth at Adolescence, 2nd ed. Oxford: Blackwell Science, 1962. This book is recognized as Tanner's landmark publication and one of the core reference works within the field of human growth and development. Although the title suggests a concentration on adolescent growth, the book actually covers a broader age range. It is also includes an important section on growth assessment techniques.

Tanner JM. Foetus into Man, 2nd ed. Ware, UK: Castlemead Publications, 1989. Tanner's short volume initially was published by Open Books (1978) with an American edition by Harvard University Press (1990) and the second edition by Castlemead. This is a comprehensive, although somewhat superficial, coverage of human growth from conception to maturity. I have used it to great effect as a recommended basic text for undergraduates, but it needs to be heavily supplemented by more up-to-date, detailed, research material.

Tanner JM. History of the Study of Human Growth. New York: Academic Press, 1988. This is the most detailed account of the history of research into the growth and development of children, told by the acknowledged British expert in human growth in the second half of the twentieth century. A common library resource, it helps put the study of human growth into a historical and social context.

Tanner JM, Whitehouse RH. Human Growth and Development. London: Academic Press, 1980. Unlikely to be found outside a library because of its cost, this is a magnificent report on almost 50 years of research by James Tanner and Reg Whitehouse from London University. Within this reference work, the growth and development of many normal children and those with growth disorders are described in detail. Each double-page spread contains growth charts, photographs, and a discussion of the pattern of growth and the etiology, diagnosis, treatment, and prognosis of those children with growth disorders.

Thompson, D'AW. On Growth and Form, new ed. Cambridge: Cambridge University Press, 1942. This is a classic. D'Arcy Thompson was known as both a scholar and author of considerable talent. It should be read for its historical contribution to the biology of human growth and development.

Ulijaszek SJ, Johnston FE, Preece MA. The Cambridge Encyclopaedia of Human Growth and Development. Cambridge: Cambridge University Press, 1998. This is an excellent reference resource, to be found in many university libraries. It is still relatively recent and ideal as an initial source of material with extensive references.